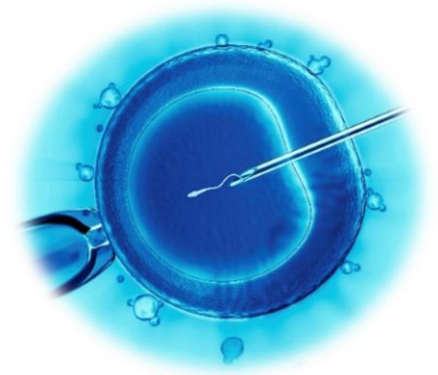


Do women offered assisted reproduction technologies have a higher incidence of gynecologic cancer? A systematic review and meta-analysis

接受輔助生殖技術的婦女，會增加婦癌發生機率嗎??

報告者：斯莉婷

日期：107年1月9日



介紹-1

Background

- 台灣人工生殖年齡分佈

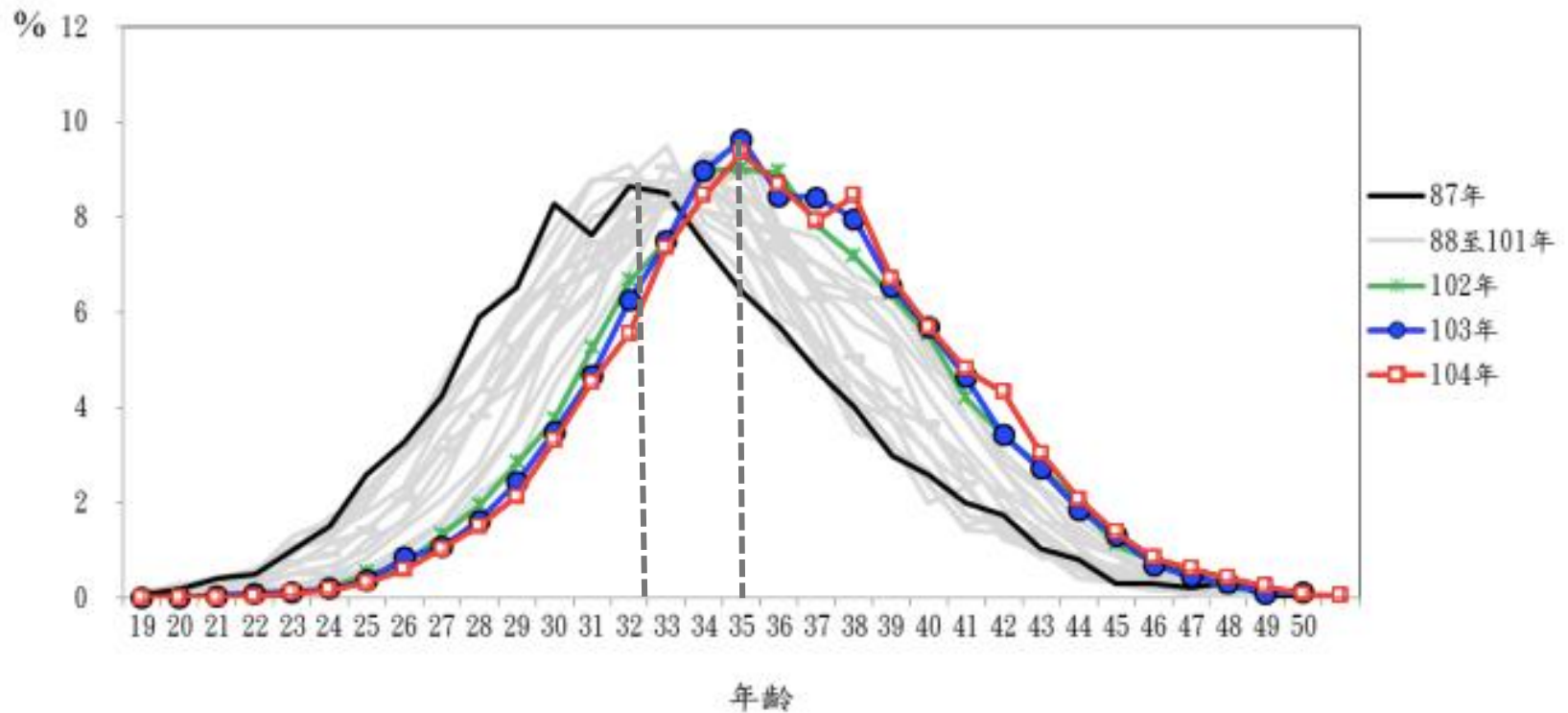
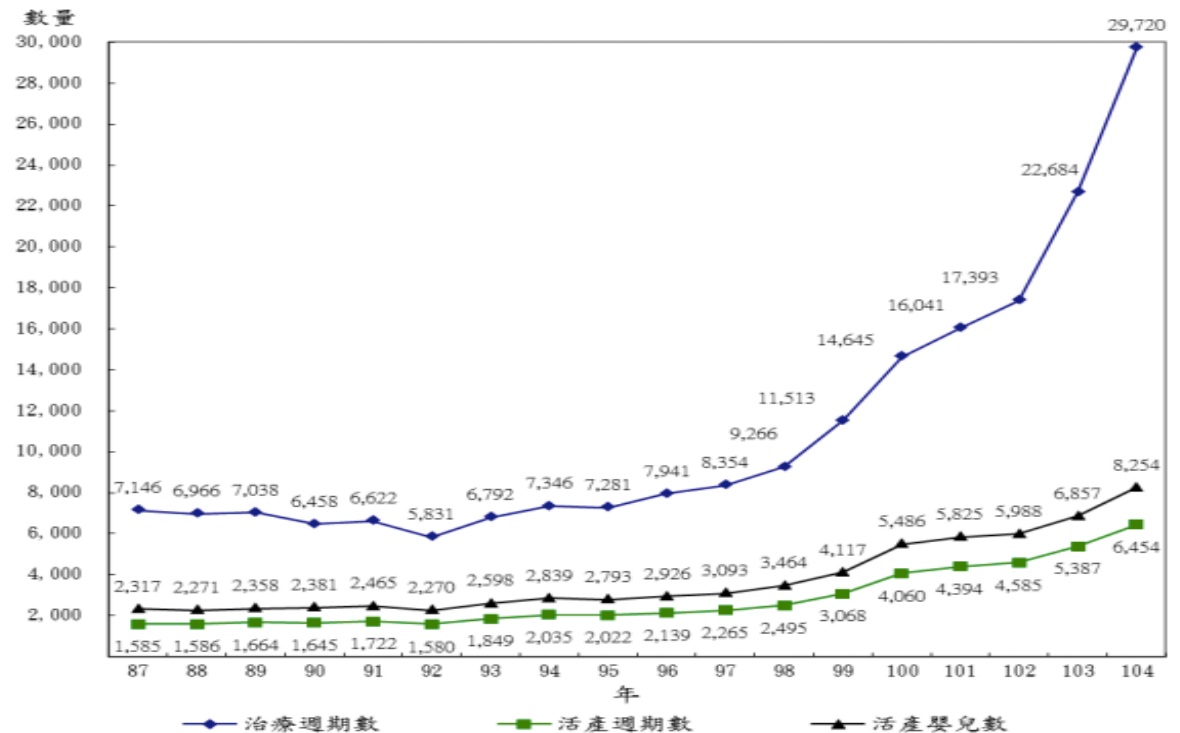


圖 19 87 年至 104 年人工生殖受術妻之年齡百分比分布

介紹-2

Background

- 1990-2009年，智利進行ART週期數量，增加超過800%，235至1932例 (Schwarze et al.,2010)
- 87年-104年台灣人工生殖治療週期數



介紹-3

Background

- ART (Assisted. Reproductive Technology) -以醫療程序將男性和女性的配子離開體內操作 (Luke et al.,2015).
- 卵巢經由促性腺激素刺激，會誘導多個卵泡發育，讓血液中雌二醇 (Estradiol , E2) 高達五倍成長 (Zhao *et al.*, 2015) 。
- 卵巢的刺激藥物又與婦科癌症有關，特別是卵巢癌，子宮內膜癌和子宮頸癌 (Sirstatidis et al., 2013) 。
- 癌症危險因素與不孕婦女的特徵共存 (低產次，高齡生產，初次月經較早，更年期較晚，母乳哺餵發生率低和持續時間短) (Luke *et al.*, 2015).

輔助生殖技術

- IVF-TE：體外受精與胚胎移植，通稱為試管嬰兒。
- 過程為取出卵子和精子，在體外受精，發展為早期胚胎，再由子宮頸口植入子宮內。
- ICSI-TE：單一精蟲顯微授精。
- 將單隻精子注射到卵質內，使精卵結合受精的方法。



步驟 1：系統性文獻回顧探討的問題為何？-1

p	women
i	assisted reproductive technologies (ART) IVF-TE (體外受精/胚胎植入術) ICSI-TE(單一精蟲顯微授精/胚胎植入術)
c	spontaneous conceptions
o	cancer risk (ovarian cancer , endometrial cancer, cervical cancer, uterine cancer, breast cancer)

步驟 2: 系統性文獻回顧的品質如何? (FAITH)

F—研究是否找到 (Find) 所有的相關證據?

最好的狀況是?

良好的文獻搜尋至少應包括二個主要的資料庫(如: Medline, Cochrane 考科藍實證醫學資料庫, EMBASE 等), 並且加上文獻引用檢索(參考文獻中相關研究、Web of Science, Scopus 或 Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文, 並且應同時使用 MeSH 字串及一般檢索詞彙(text words)。

- A search based on keywords "*in vitro* fertilization"; "*in vitro* fertilisation"; "controlled ovarian stimulation"; "Assisted Reproductive Technology"; "IVF" or "ICSI"; "cancer risk"; "ovarian cancer", "endometrial cancer", "cervical cancer", "uterine cancer", "breast cancer"
- Carried out on [NICE](#), [Medline](#) and [Trip Database](#). These keywords were [combined](#) using the word [AND](#) to generate a subgroup relevant to the search.

步驟 2: 系統性文獻回顧的品質如何? (FAITH)

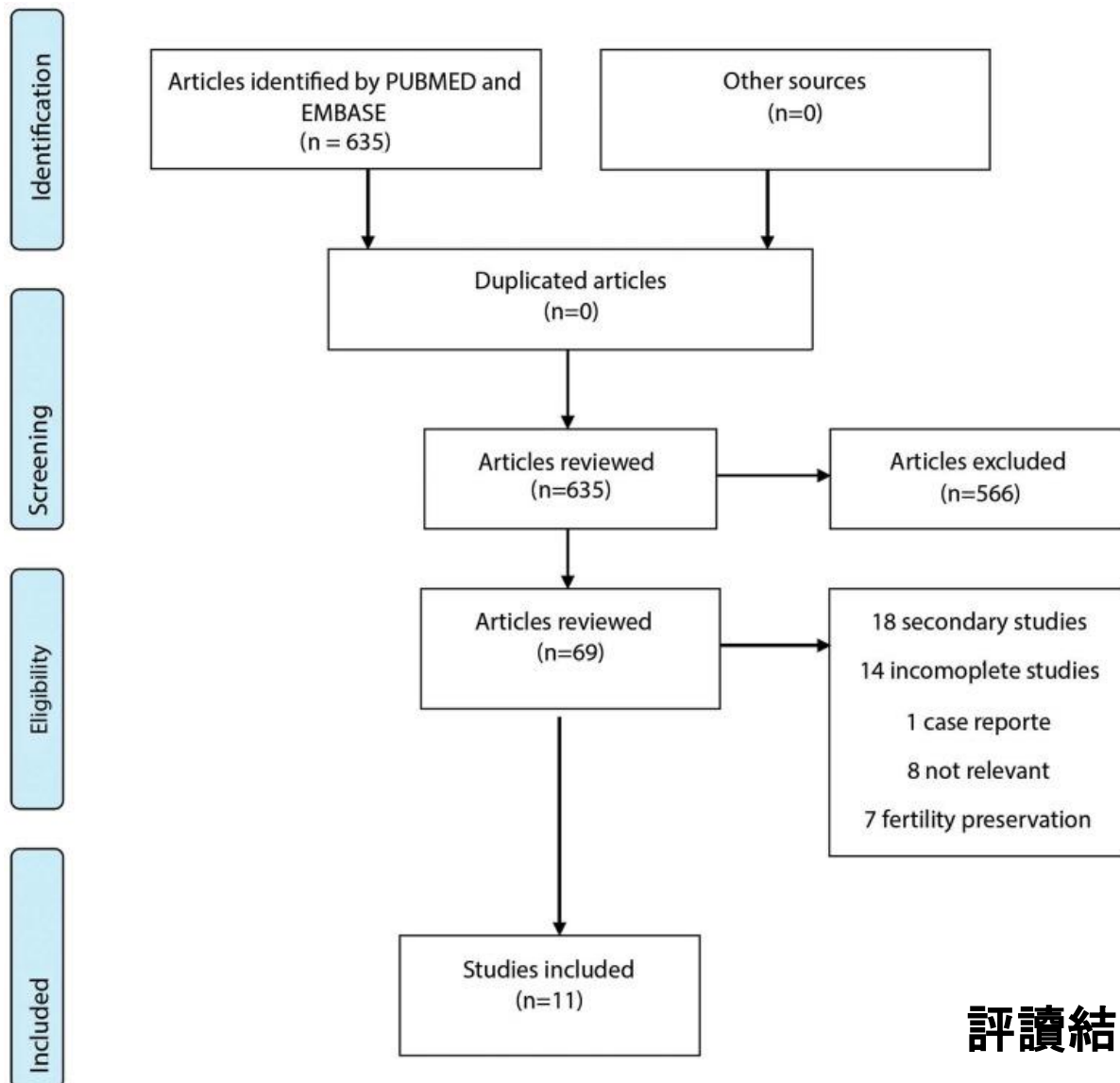
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- Studies written in **English** and **Spanish** published between **June 2000 and June 2016** comparing pregnancies achieved by **IVF-TE, ICSI-TE** vs. **spontaneous conceptions** were **included**.
- Case reports, case series, meta-analysis, and systematic reviews were **excluded**.
- Studies enrolling patients with a history of BRCA1 or BRCA2 mutation, animal studies, studies evaluating fertility preservation in patients diagnosed with cancer, and studies referring to other types of cancer were **excluded**.

步驟 2: 系統性文獻回顧的品質如何? (FAITH)



評讀結果: ☒ 是 ☐ 否 ☐ 不清楚

步驟 2: 系統性文獻回顧的品質如何? (FAITH)

A—文獻是否經過嚴格評讀 (Appraisal) ?

最好的狀況是？應根據不同臨床問題的文章類型，選擇適合的評讀工具，並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)

- Two authors (JES and PV) reviewed these papers to check whether they met the inclusion and exclusion criteria.
- Statistical package Stata (Statacorp, USA) was used to treat the meta-analysis data.
- Heterogeneity between studies was assessed by the chi-square test.
- A fixed-effect model was used for the meta-analysis and odds ratios (OR) were calculated with a 95% confidence interval (95% CI) using the Mantel-Haensze test. The results were represented in a forest plot.

評讀結果：■是 □否 □不清楚

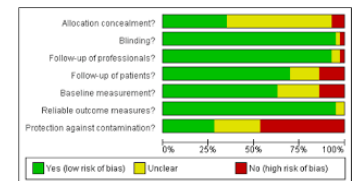
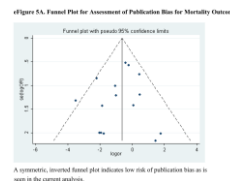
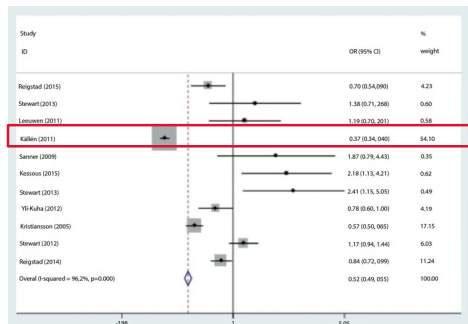
步驟 2: 系統性文獻回顧的品質如何? (FAITH)

一是否只納入 (included) 具良好效度的文章？

最好的狀況是？

僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有一項研究結果是極小偏誤的試驗。

- Three of the 11 papers included in our review looked into the overall risk of different types of cancer, including gynecologic tumors
- three assessed the risk of ovarian cancer and two assessed exclusively the risk of gynecologic cancer subsequent to ART procedures.



評讀結果：☐是 ☐否 ☒不清楚

Table 1. Summary of articles included

Author	Methodology	Principal findings
Kristiansson <i>et al.</i> , 2007	Prospective cohort analysis performed in Sweden between 1981-2001	No increase in the risk of developing postmenopausal cancer in women with a delivery after IVF compared with controls
Sanner <i>et al.</i> , 2009	Retrospective cohort analysis of 2,768 women with infertility treatment between 19761-1975. The main comparison was the use of gonadotropins and clomiphene citrate.	Five-fold increase in the risk of cancer in women who took gonadotropins
Källén <i>et al.</i> , 2011	Retrospective cohort analysis of women with delivery after IVF between 1982-2006. Cases of gynecologic cancer were found by cross-referencing the patients in the cohort against the Cancer Database.	Low risk of breast and cervical cancer. No change in the risk of other types of cancer.
van Leeuwen <i>et al.</i> , 2011	Retrospective cohort analysis	Data suggest an increase of cancer after controlled ovarian hyperstimulation
Yil-Kuha <i>et al.</i> , 2012	Retrospective cohort analysis of 18,350 Finnish women treated between 1996-1998. Cancer cases were identified from a cancer database	Three-fold increase in the risk of ovarian cancer in women offered IVF.
Stewart <i>et al.</i> , 2012	Retrospective cohort analysis performed in Australia between 1982-2002	Increased risk of breast cancer in women offered ART at younger ages
Stewart <i>et al.</i> , 2013	Retrospective cohort analysis of 21,639 Australian patients diagnosed with infertility or offered infertility treatment; the individuals were cross-referenced to a cancer database	Women with a history of ART are at higher risk of having borderline ovarian tumors.
Stewart <i>et al.</i> , 2013	Retrospective cohort analysis in Australia, between 1982-2002	No evidence of increased risk of ovarian cancer after post-IVF delivery.
Reigstad <i>et al.</i> , 2015	Retrospective cohort analysis of 808,834 Norwegian women after delivery, linked to the national cancer database. (1984-2010)	Increased risk of breast cancer in women with post-ART deliveries <i>versus</i> women with spontaneous conception delivery.
Reigstad <i>et al.</i> , 2015	Retrospective cohort analysis of 806, 248 women registered in the Norway Birth Register between 1984 and 2010. Gynecologic tumors were identified by cross-referencing the enrolled individuals to the Cancer Database	Increased risk of cancer after ART; however, after correction for confounding factors, the difference was not significant.
Kessous <i>et al.</i> , 2016	Retrospective cohort study of 106,031 Israeli women with a history of either IVF or ovulation induction.	Increased risk of gynecologic cancer in women with history of IVF

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年代	P	I	C	O	追蹤
Kristiansson (2007)	<ul style="list-style-type: none"> 1981-2001 年瑞典 n=64 8775 	<ul style="list-style-type: none"> 有IVF(n= 8,716) 	<ul style="list-style-type: none"> 沒有IVF (n=640,059) 	<ul style="list-style-type: none"> IVF治療後分娩的婦女發生癌變的風險沒有增加 ART術後觀察到原位癌或導管癌的發生率較低 (OR : 0.570; 95%CI : 0.503-0.646) 	<ul style="list-style-type: none"> 實驗組(32.8歲)追蹤6年 對照組(26.7歲)追蹤7-8年
Sanner (2009)	<ul style="list-style-type: none"> 1961-1975 年瑞典 n=27 68 	<ul style="list-style-type: none"> 有IVF(n=1,615) HIT=389 (34%) clomiphene citrate=325 (28%) gonadotropins (GDT) =439 (38%) 	<ul style="list-style-type: none"> 沒有IVF (n=1,153) 	<ul style="list-style-type: none"> 接觸促性腺激素而發展為癌症的風險增加5-6倍 (OR : 1.873; 95%CI : 0.793-4.427) 	<ul style="list-style-type: none"> 結束時的平均年齡為27歲(範圍16-45歲) 追蹤時間33年(中位數)
Källén (2011)	<ul style="list-style-type: none"> 1982-2006 年瑞典出生登 	<ul style="list-style-type: none"> 有IVF(n=24,058) 	<ul style="list-style-type: none"> 沒有IVF (n=1,394,061) 	<ul style="list-style-type: none"> 接受IVF治療的嬰兒與自然受孕後分娩嬰兒的婦女的病例，發現IVF組患乳腺癌或宮頸癌的風險較低 (OR : 0.369; 95%CI : 0.344-0.396)。 	<ul style="list-style-type: none"> 體外受精後第一次分娩的平均年齡為32歲 追蹤結束時的平均年齡為40.3歲 平均追蹤時間8.3年

Table 1. Summary of articles included

van Leeuwen <i>et al.</i> , 2011	Retrospective cohort analysis	Data suggest an increase of cancer after controlled ovarian hyperstimulation
Yli-Kuha <i>et al.</i> , 2012	Retrospective cohort analysis of 18,350 Finnish women treated between 1996-1998. Cancer cases were identified from a cancer database	Three-fold increase in the risk of ovarian cancer in women offered IVF.
Stewart <i>et al.</i> , 2012	Retrospective cohort analysis performed in Australia between 1982-2002	Increased risk of breast cancer in women offered ART at younger ages

年代	P	I	C	O	追蹤
van Leeuwen (2011)	<ul style="list-style-type: none"> 1983 - 1995年 荷蘭 n=25,152 	<ul style="list-style-type: none"> 至少接受過一次IVF週期 (n=19,146) 	<ul style="list-style-type: none"> 未接受試管嬰兒治療的不孕症婦女 (n=6,006) 	<ul style="list-style-type: none"> 卵巢刺激IVF可能會增加惡性卵巢腫瘤的風險，特別是交界型卵巢腫瘤 (OR : 1.187; 95%CI : 0.702-2.005)。 	<ul style="list-style-type: none"> 追蹤14.7年 (中位數)
Yli-Kuha (2012)	<ul style="list-style-type: none"> 1996 – 1998年 芬蘭 癌症登記 	<ul style="list-style-type: none"> ICSI和FET治療 (n = 9,175) 	<ul style="list-style-type: none"> 未接受治療的婦女 (n = 9,175) 	<ul style="list-style-type: none"> 現IVF組卵巢癌發病率比對照組高3倍。兩組的交界性腫瘤發生率相似 (OR : 0.778; 95%CI : 0.604-1.002) 	<ul style="list-style-type: none"> 追蹤7.9年
Stewart (2012)	<ul style="list-style-type: none"> 1983 - 2002年 澳州 20-44歲的原發性和繼發性不孕的婦女 (n =21,025) 	<ul style="list-style-type: none"> IVF n=7,381 	<ul style="list-style-type: none"> 未接受治療的婦女 n=13,644 	<ul style="list-style-type: none"> 年輕時開始接受IVF治療的婦女女性乳腺癌的比例增加 40歲開始接受IVF治療的婦女中，危險比率沒有升高，無法發現乳腺癌與晚期使用IVF (OR : 1.166; 95%CI : 0.944-1.441) 之間的正相關性。 	<ul style="list-style-type: none"> 首次不孕年齡<31歲 平均隨訪時間17.5年 (95%CI 17.4-17.6) 乳腺癌診斷的平均年齡為47歲，絕大多數癌症 (佔總數的73%) 在≤50歲診斷

Table 1. Summary of articles included		
Stewart <i>et al.</i> , 2013	Retrospective cohort analysis of 21,639 Australian patients diagnosed with infertility or offered infertility treatment; the individuals were cross-referenced to a cancer database	Women with a history of ART are at higher risk of having borderline ovarian tumors.
Stewart <i>et al.</i> , 2013	Retrospective cohort analysis in Australia, between 1982-2002	No evidence of increased risk of ovarian cancer after post-IVF delivery.
Reigstad <i>et al.</i> , 2015	Retrospective cohort analysis of 808,834 Norwegian women after delivery, linked to the national cancer database. (1984-2010)	Increased risk of breast cancer in women with post-ART deliveries versus women with spontaneous conception delivery.

年代	P	I	C	O	追蹤
Stewart (2013)	<ul style="list-style-type: none"> 1982 – 2002年澳洲 n=21,639 	<ul style="list-style-type: none"> 接受試管嬰兒的婦女 n=7455 	<ul style="list-style-type: none"> 沒有接受試管嬰兒的婦女 n=14,095 	<ul style="list-style-type: none"> 沒有證據顯示IVF組患者卵巢癌風險增加 (OR : 2.413; 95%CI : 1.152-5.054) 。 	<ul style="list-style-type: none"> 隨蹤開始時平均年齡和中位數年齡31 歲; 結束時48歲。 追蹤時間平均17 年。 33歲到61歲之間的人群中發現了卵巢癌; 平均年齡為46 歲。
Stewart (2013)	<ul style="list-style-type: none"> 1982 - 2002年 澳洲 n=21,639 	<ul style="list-style-type: none"> 接受試管嬰兒的婦女 n=7455 20-44歲婦女 	<ul style="list-style-type: none"> 沒有接受試管嬰兒的婦女 n=14,095 	<ul style="list-style-type: none"> 接受試管嬰兒的婦女患卵巢交界性腫瘤的風險增加 (OR : 1.376; 95 %CI : 0.706-2.683) 。 	<ul style="list-style-type: none"> 首次不孕不育症平均年齡31.2 歲，平均追蹤16.9 年。 診斷的平均年43.2 歲
Reigstad (2015)	<ul style="list-style-type: none"> 808,834 挪威癌症登記 	<ul style="list-style-type: none"> ART n=16,626 ICSI n=4968 	<ul style="list-style-type: none"> n=792,208 	<ul style="list-style-type: none"> 與自發懷孕的婦女相比，ART手術後分娩婦女患乳腺癌的風險增加 (OR : 0.844; 95%CI : 0.723-0.985) 	<ul style="list-style-type: none"> 實驗組入組時年齡中位數為32.5歲 (18.6-49.9歲)，結束40.5歲，追蹤10.6年 對照組:未接觸者為26.3 歲 (10.5-54.6歲) 結束42.1歲，追蹤16.5年

Table 1. Summary of articles included

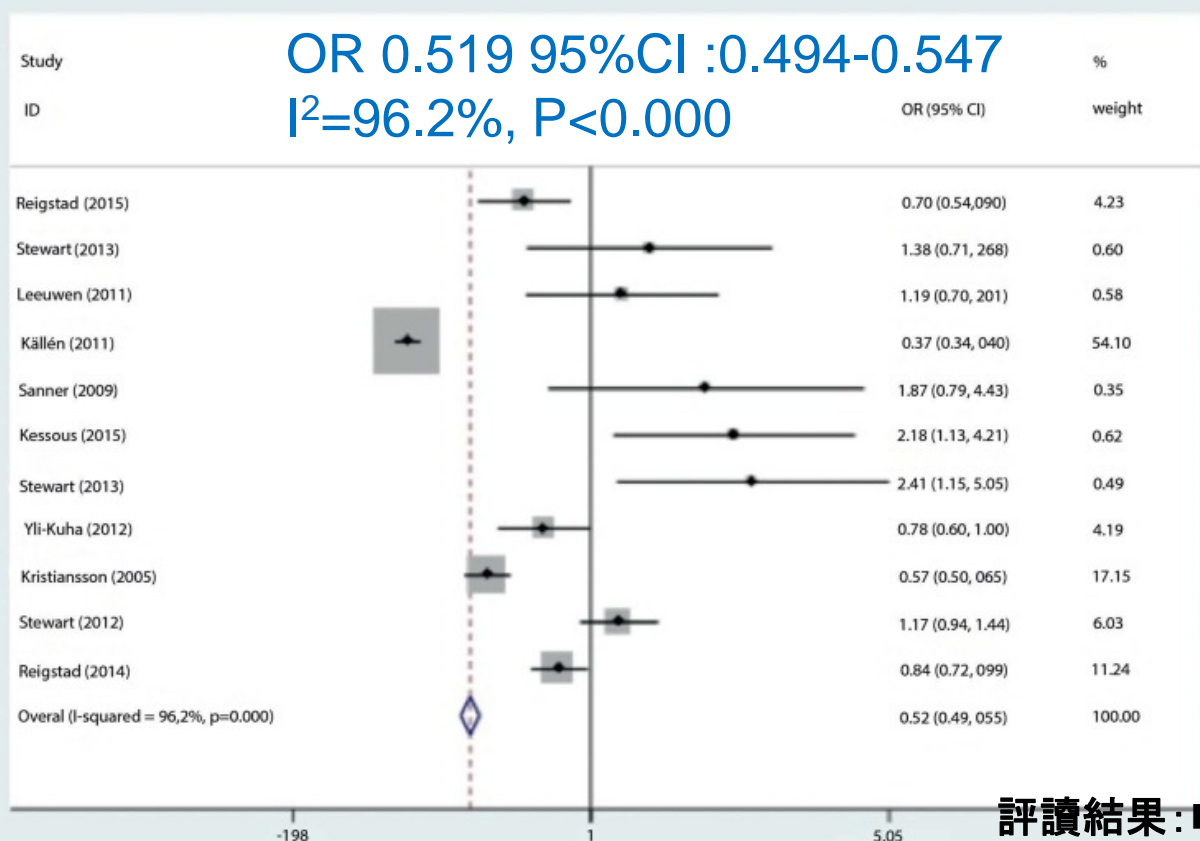
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Kessous <i>et al.</i> , 2016	Retrospective cohort study of 106,031 Israeli women with a history of either IVF or ovulation induction.	Increased risk of gynecologic cancer in women with history of IVF

年代	P	I	C	O	追蹤
Reigstad (2015)	<ul style="list-style-type: none"> 1984 -2010 年挪威 $n = 812,986$ 	<ul style="list-style-type: none"> ART女性 ($n = 4363$) 	<ul style="list-style-type: none"> 非ART女性 ($n = 789,723$) 	<ul style="list-style-type: none"> 發現一般癌症的風險增加; 然而, 多次分析校正後發現增加並不顯著 (OR : 0.697; 95%CI : 0.541-0.897)。 當排除乳腺癌和中樞神經系統癌症病例時, 我們沒有發現總體癌症風險過高, 這意味著總體癌症風險升高是由於這兩種特定癌症的風險增加。 	<ul style="list-style-type: none"> ART婦女的追蹤時間7.3年(中位數), 非ART婦女的隨訪時間為16.0年 ART婦女的乳腺癌風險增加了20% (Reigstad, 2015)。
Kessous (2016)	<ul style="list-style-type: none"> 1988 - 2013 年以色列 $n=106,031$ 	<ul style="list-style-type: none"> 生育治療 ($n = 4363$) $n = 3,214$ 接受OI $n = 1,124$ 接受IVF 	<ul style="list-style-type: none"> 沒有生育治療 ($n = 101,668$) 	<ul style="list-style-type: none"> 有IVF病史的患者與患者相比, 患卵巢癌或子宮癌的風險更高, 與排卵誘導和沒有不育史的患者 (OR : 2.181; 95%CI : 1.130-4.208)。 	<ul style="list-style-type: none"> 平均追蹤時間為12年

步驟 2: 系統性文獻回顧的品質如何? (FAITH)

T—作者是否以表格和圖表「總結」(total up) 試驗結果?

最好的狀況是? 應該用至少 1 個摘要表格呈現所納入的試驗結果。若結果相近, 可針對結果進行統合分析(meta-analysis), 並以「森林圖」(forest plot)呈現研究結果, 最好再加上異質性分析。



評讀結果: ■是 □否 □不清楚

步驟 2: 系統性文獻回顧的品質如何? (FAITH)

H—試驗的結果是否相近—異質性 (Heterogeneity) ?

最好的狀況是？在理想情況下，各個試驗的結果應相近或具同質性，若具有異質性，作者應評估差異是否顯著(卡方檢定)。根據每篇個別研究中不同的PICO及研究方法，探討造成異質性的原因。

- large number of patients from both groups and the fact that they reflect populations from different countries.
- The limitations revolve around the fact that not all studies contained detailed information on the drugs used in ART protocols, duration of treatment, number of cycles, or dosages.
- The cohorts were not equivalent, since in some studies the control groups were infertile patients, while in others controls were fertile.

評讀結果：■是 □否 □不清楚

評讀總表

研究的品質有多好(內在效度)

研究是否找到 (Find) 所有的相關證據？

評讀結果: 是

文獻是否經過嚴格評讀 (Appraisal)？

評讀結果: 是

是否只納入 (included) 具良好效度的文章？

評讀結果: 不清楚

作者是否以表格和圖表「總結」 (total up) 試驗結果？

評讀結果: 是

試驗的結果是否相近－異質性 (Heterogeneity)

評讀結果: 是

能依系統性文獻回顧之結論回答婦女的問題嗎？

輔助生殖技術婦女不會增加婦科癌症的發生機率？



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不同意 0票



Thank You