Risks of ovarian, breast and corpus uteri cancer in women treated with assisted reproductive technology; 2.2 million person years of observation in Great Britain

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ABSTRACT:

Objectives: Exposure to supra-physiological hormone levels and multiple ovarian punctures might increase cancer risks in women following assisted reproduction, however risks remain uncertain. This study aimed to investigate risks of corpus uteri, breast and ovarian cancer in women who have had assisted reproduction.

Design: Large population based data-linkage cohort study.

Setting & Participants: All women who had assisted reproduction in Great Britain, 1991-2010, as recorded by the Human Fertilisation & Embryology Authority (HFEA).

Interventions: HFEA fertility records for cohort members were linked to national cancer registrations.

Main outcome measures: Observed first diagnosis of corpus uteri, breast or ovarian cancer in cohort members are presented in comparison with age, sex and period specific expectation. Standardized Incidence Ratios (SIRs) were calculated using age, sex and period-specific national incidence rates.

Results: 255,786 women contributed 2,257,789 person-years follow-up. No significant increased risk of corpus uteri cancer (164 cases observed compared to 146.9 cases expected; SIR 1.12; 95% Confidence Interval (CI) 0.95-1.30) was found during an average of 8.8 years follow-up. This study found no significant increased risks of breast cancer overall (2578 observed vs 2641.2 expected; SIR 0.98; 95%CI 0.94-1.01) or invasive breast cancer (2272 observed vs 2371.4 expected; SIR 0.96; 0.92-1.00). An increased risk of in-situ breast cancer (291 observed vs 253.55 expected; SIR 1.15; 1.02-1.29; absolute excess risk (AER) 1.7 cases per 100,000 person-years) was detected, associated with increasing number of treatment cycles (*P*=0.03). There was an increased risk of ovarian cancer (405 observed vs 291.8 expected; SIR 1.39; 1.26-1.53; AER 5.0 cases per 100,000 person-years), both invasive (264

observed vs. 188.1 expected SIR 1.40; 1.24-1.58; AER 3.4 cases per 100,000 person-years) and borderline (141 observed vs.103.7 expected; SIR 1.36; 1.15-1.60; AER 1.7 cases per 100,000 person-years). Increased risks of ovarian tumours were limited to women with endometriosis, low parity, or both. This study found no increased risk of any ovarian tumour in women treated because of only male factor or unexplained infertility.

Conclusions: No increased risk of corpus uteri or invasive breast cancer was detected, but increased risks of in-situ breast cancer and invasive and borderline ovarian tumours were found in this study. Our results suggest that ovarian tumour risks may be due to patient characteristics, rather than assisted reproduction *per se,* although both surveillance bias and the effect of treatment are also possibilities. Ongoing monitoring of this population is essential.

What this paper adds

What is already known on this subject: Risks of reproductive cancers in women who have undergone assisted reproduction procedures are uncertain. Some but not all previous studies suggest possible increased risk of breast cancer in women treated at younger ages and with multiple cycles. Previous studies investigating endometrial cancer risk are underpowered. Early studies suggested increased risks of ovarian cancer in these women, whilst more recent studies are more reassuring, although inconsistent regarding any increase in borderline ovarian tumours.

What this study adds: This population-based study is the largest such study to date. Endometrial cancer was not increased in women who have had assisted reproduction when compared to the general population. There was no increased risk of breast cancer overall, nor invasive breast cancer, but a small increase in in-situ breast cancer. Increased risks of ovarian cancer, both invasive and borderline, were observed but limited to women with other known risk factors. These findings require further investigation.

INTRODUCTION:

Assisted reproduction cycles usually involve exposure to supra-physiological levels of oestradiol, exogenous gonadotropins and multiple ovarian punctures, all potentially carcinogenic[1 2] . Most concern surrounds risks of breast, endometrial and ovarian cancers after such exposures [3-16].

Studies investigating breast cancer risks in women who underwent assisted reproduction are inconsistent[3-12]. Although some studies have shown an increased risk [17], most studies do not show an overall increased of breast cancer in exposed women [3-5 7 8 10]. However, some suggest possible increased risk within subgroups[8 9], including women treated at younger ages[9] and with multiple cycles[8]. Most studies investigating endometrial cancer risk in exposed populations have not found a significant increased risk [3 4 6 7 18]. However, most studies have provided very imprecise estimates due to small sample size and few events [3 4 6 18]. One study suggested an increased risk of endometrial cancer associated with exposure to Gonadotrophins, commonly used as part of ART [19]. Some early studies investigating fertility drugs used alone, such as single agent oral clomiphene, suggested increased risks of ovarian cancer[20]. Others found no association between fertility drug and ovarian cancer risk[21]. Recent investigations into their use as part of assisted reproduction have generally been more reassuring, but remain inconsistent and at risk of bias [4 5 11]. Some [13 14], but not all studies[6] have found an increase in borderline tumours.

Given previous inconsistent results, small study size, and lack of information on potential confounders, we undertook a population-based linkage study in Britain to provide risk estimates for breast, corpus uteri and ovarian cancer, in a cohort of over 266,000 women

undergoing assisted reproduction, with information on potential confounders such as parity and infertility diagnosis.

METHODS:

STUDY POPULATION

We defined assisted reproduction as 'treatments or procedures that include in vitro handling of both human oocytes and sperm or embryos, for the purpose of reproduction'[22]. Records for all women undergoing assisted reproduction, January 1991 to September 2009, and those undergoing the same, October 2009 to December 2010 who gave their prospective consent, in England, Wales and Scotland were obtained from the Human Fertilisation and Embryology Authority (HFEA).

UK law mandates reporting of all assisted reproduction cycles to the HFEA. For cycles performed before October 2009, research use of these data was permitted, but consent could be withdrawn retrospectively. 0.3% of the cohort had done so before this study began. The study cohort, January 1991 to September 2009, therefore represents 99.7% of the at-risk population. For cycles performed October 2009 onwards, prospective consent was required. Overall consent was not provided for 7% of women undergoing assisted reproduction, 1991-2010, who were therefore not included in this study, representing a loss of less than 1% of person-years follow-up (*Supplementary appendix*).

PATIENT INVOLVEMENT & STUDY APPROVAL

Representatives from patient support groups (Fertility Network UK) were consulted on the original research question, design and planning of this study. Approval of the study and

waiver of the requirement for individual consent were obtained from the UK Health Research Authority Confidentiality Advisory Group and London Research Ethics Committee (References 5.04(b)/10 & 10/H0720/18 respectively). Given the anonymous nature of the final dataset, it is not possible to disseminate results to individual study participants; instead results will be shared with fertility practitioners and clinics through the Human Fertility & Embryology Authority networks.

OUTCOME DATA

HFEA records were linked to the National Health Service Central Registers of England, Wales, and Scotland (from which emigrations, deaths and cancer registrations are reported to authorised medical researchers) in a one-off linkage. Completeness and accuracy of these registers have been described[23-25]. Overall, records of 266,787 eligible women (95.1%) were linked (*Supplementary appendix*). Cancer diagnosis date, topography code (ICD9/ICD10), morphology (ICD-O-2/ICD-O-3), and behaviour (ICD-O-2/ICD-O-3), were available where an incident cancer was diagnosed. Women with cancer diagnoses (including non-melanoma skin cancer), recorded prior to first treatment year were excluded from analyses. Data relating to potential confounding factors such as infertility diagnosis, parity (as recorded at last treatment cycle completion) and to treatment details including number of stimulated cycles and age at first treatment were obtained for each cohort member from the HFEA database. These data are a combination of patient self-reported and clinic reported (*Table S1 Supplementary appendix*). Information regarding infertility diagnoses are reported to the HFEA by assisted reproduction clinics, based on investigations undertaken by that clinic, the referring clinician or rarely patient self-report.

STATISTICAL ANALYSES

Follow-up was calculated from date of first treatment (estimated as mid-point of first treatment year), until date of any cancer diagnosis, death, emigration or study end (March 2011), whichever came first. For analyses involving number of cycles, infertility duration, live and multiple births, person-years at risk were calculated from date of last treatment (estimated as mid-point of last treatment year), as the HFEA did not record intermediate dates required for time dependent analysis. Expected cancers were calculated multiplying person-years at risk by corresponding national incidence rates (by 5-year age band and individual calendar year) for the general female population of England & Wales. Standardized incidence ratios (SIR) were calculated comparing observed to expected values. 95% confidence intervals, 2-sided *P*-values and trends were calculated assuming a Poisson distribution[26]. Sensitivity analyses excluded the first 12 months of follow-up (*Supplementary appendix*). Absolute excess risks (AER) represent an estimate of the increased risk in the study group as compared with the general population and gives a direct measure of excess risk; they are presented per 100,000 person-years. Analyses were performed using STATA, version 12[27].

RESULTS:

CHARACTERISTICS OF STUDY PARTICIPANTS:

255,786 women contributed 2,257,789 person-years follow-up. Average follow-up was 8.8 years with 41% followed for ≥10 years. Average age at first treatment was 34.5 years. Infertility cause involved at least one female factor in 44% (including endometriosis; ovulatory disorders- predominantly polycystic ovary disease; and tubal disease). Infertility was unexplained in 19% of women and due only to male factor in 33%. Average infertility duration was 4.9 years. Women had 1.8 stimulated cycles on average, only 20% having >2 stimulated cycles. Approximately half had at least one live birth after treatment completion (*Table 1*).

BREAST CANCER

There was no overall increased risk of breast cancer (2578 observed vs. 2641.2 expected cancers; SIR 0.98; 95%CI 0.94-1.01; Absolute excess risk (AER) -2.8 cases per 100,000 person-years (95%CI -7.1, 1.8); *Table 2*). 76% of tumours were ductal carcinomas (n=1,963), 9% lobular (n=228), 12% other epithelial tumours (n=319), and 3% non-epithelial or unspecified (n=68). There were also no significant raised risks in strata by age at first treatment, infertility duration, number of stimulated cycles, number of live births and multiple births. There were significant risk reductions with increasing duration since treatment completion (*P*=0.01; *Table 3*), and in women with any female factor or only male factor infertility (*Table 3*), but no difference between risks at pre and post-menopausal ages separately (age: <50 years, SIR=0.98; 0.94-1.02; ≥50 years, SIR=0.97; 0.89-1.06; *data not shown*). Excluding the first 12 months follow-up, breast cancer risk was significantly reduced compared with age-

standardized expectation (SIR 0.95; 0.92-0.99, *P*=0.02; *Supplementary appendix*). There was no increased risk of invasive breast cancer (SIR 0.96; 0.92-1.00; AER -4.4 cases per 100,000 person-years (95%CI -8.5, -0.2); *Table 4*) but a small increased risk of in-situ breast cancer (SIR 1.15; 1.02-1.29; AER 1.7 cases per 100,000 (95%CI 0.2, 3.2); *Table 4*), which was associated with number of treatment cycles (*P*=0.03). Excluding the first 12 months follow-up did not substantially change results for in-situ breast cancer risk (*Supplementary appendix*).

CARCINOMA OF THE CORPUS UTERI

Corpus uteri cancer risk was not significantly raised (SIR 1.12; 0.95-1.30; AER 0.8 cases per 100,000 (95%CI -0.3, 2.0); *Table 2*). Over 92% (n=152) of corpus uteri tumours were epithelial, 70% (n=107) of which were endometrioid. 8% were non-epithelial or unspecified (n=12). Significantly increased risk was observed in women with an ovulatory disorder (SIR 1.59; 1.13-2.17; *Table 3*). There was a highly significant trend of increasing risk with decreased parity (*P*<0.001) and having a multiple birth significantly decreased risk (SIR 0.42; 0.14-0.99; *Table 3*). No significant variation in risk was noted with number of cycles (*P*=0.93), age at first treatment (*P*=0.28) or duration since treatment completion (*P*=0.12). Excluding the first 12 months follow-up did not substantially change results (*Supplementary appendix*).

OVARIAN CANCER

An overall increased risk of ovarian cancer was observed (SIR 1.39; 1.26-1.53; AER 5.0 cases per 100,000 person-years (95%CI 3.3, 6.9); *Table 2*). Increased risks were seen across most age groups at first treatment, but there was a highly significant trend of increasing risk with decreasing age at first treatment (*P*<0.001;*Table 3*). Significantly increased risks were found

in women who had any diagnosis of female factor infertility (SIR 1.66; 1.46-1.88; *Table 3*), particularly endometriosis (SIR 2.31; 1.74-3.01; *Table 3*) or tubal disease (SIR 1.68; 1.43-1.97; *Table 3*). No increased risk was seen where infertility was male factor only (SIR 1.05; 0.85-1.27) or unexplained (SIR 0.96; 0.69-1.31; *Table 3*). There was a significant trend of decreasing risk with increasing number of live births (*P*=0.001; *Table 3*): remaining nulliparous after treatment completion conferred highest risk (SIR 1.57; 1.37-1.79; *Table 3*). No increased risk was seen with increasing infertility duration (*P*=0.15), number of cycles (*P*=0.86) or duration since treatment completion (*P*=0.74). Excluding the first 12 months follow-up did not substantially change results (*Supplementary appendix*).

When tumours were classified as invasive or borderline, significant excesses of both were noted (SIR 1.40; 1.24-1.58; AER 3.4 cases per 100,000 person years (2.0, 4.9) and SIR 1.36; 1.15-1.60 respectively; AER 1.7 cases per 100,000 person years (0.7, 2.8); *Table 4*).

INVASIVE OVARIAN TUMORS

There was a significant trend of increasing risk of invasive ovarian tumours with decreasing age at first treatment (*P*=0.02; *Table 4*). Significantly increased risks were detected in women who had any diagnosis of female factor infertility (SIR 1.66; 1.41-1.94; *Table 4*), particularly endometriosis (SIR 2.47; 1.75-3.39; *Table 4*) or tubal disease (SIR 1.71; 1.40-2.08; *Table 4*). Risk significantly decreased with increasing parity (*P*=0.001): women nulliparous after treatment completion were at greatest risk (SIR 1.67, 1.42-1.95; *Table 4*). There was no significant variation in risk with number of cycles (*P*=0.29), infertility duration (*P*=0.25) or duration since treatment completion (*P*=0.44), nor was risk raised in women treated for male factor only infertility (SIR 1.09, 0.84, 1.39). 33% of invasive ovarian tumours were serous (n=87), 25% endometrioid (n=66), 8% mucinous (n=22), 18% other or unspecified

epithelial tumours (n=45), and 17% non-epithelial or unspecified (n=44). Excluding the first 12 months follow-up did not substantially change results.

BORDERLINE OVARIAN TUMORS

Significantly increased risks of borderline ovarian tumour was associated with decreasing age at first treatment (*P*<0.001; *Table 4*) and any diagnosis of female factor infertility (SIR 1.66; 1.33-2.05; *Table 4*), particularly endometriosis (SIR 2.03; 1.18-3.25; *Table 4*), or tubal disease (SIR 1.62; 1.21-2.12; *Table 4*). Risk did not change significantly with number of cycles (*P*=0.18), parity (*P*=0.34), infertility duration (*P*=0.42), or duration since treatment completion (*P*=0.84), nor was risk raised in women treated for male factor only infertility (SIR 0.96, 0.66, 1.35). 45% of borderline tumours were serous (n=64), 34% mucinous (n=48), <2% endometrioid (n<5), <2% other or unspecified epithelial tumours (n<5), and 18% non-epithelial or unspecified (n=25). Excluding the first 12 months follow-up reduced the risk of borderline ovarian tumour (SIR 1.19; 0.98-1.43; *Supplementary appendix*) and risk in relation to endometriosis (SIR 1.57; 0.81-2.73; *Supplementary appendix*).

OVARIAN CANCER RISK STRATIFIED BY RISK FACTORS

Parous women who did not have a diagnosis of endometriosis did not have an increased risk of ovarian cancer overall (SIR 1.03; 0.86-1.22; *Table 5*), invasive (SIR 1.03; 0.82-1.27; *Table 5*), or borderline tumours (SIR 1.02; 0.75-1.35; *Table 5*). Risks of all types of ovarian cancer were raised in nulliparous women who did not have a diagnosis of endometriosis but to a lesser extent than in parous women with endometriosis (*Table 5*). Women who were nulliparous with a diagnosis of endometriosis had greater risk of invasive ovarian tumour (SIR 2.64; 1.69-3.93; *Table 5*) than women with just one of these risk factors. In contrast,

nulliparous women with endometriosis had no significant risk of a borderline tumour (SIR 1.47; 0.59-3.04; *Table 5*), though nulliparity and endometriosis were each separately associated with increased risk (*Table 5*). The significant association between decreasing age at first treatment and increasing risk of invasive ovarian tumour was present in women with at least one of endometriosis or nulliparity ($P<0.001$), but not in those without either (P=0.62); however these analyses were based on small numbers (*Supplementary appendix*).

DISCUSSION:

Assisted reproduction is practiced worldwide and more than 5 million children have been born as a result[28]. It is important to establish related disease risks for affected individuals, public health systems, and for counselling of potential patients. In this large population-based cohort, we found no overall increased risk of breast cancer, consistent with most[3-7 9 10] but not all[12] published studies. We found no significant association between risk of breast cancer and age at first treatment, in contrast to a small number of earlier studies[8 9 29]. Reasons for significant decreases in breast cancer risk seen in some sub-analyses, such as women who had assisted reproduction for female factor infertility, are unclear. These may reflect beneficial levels of lifestyle-related risk factors for breast cancer[30 31]. Unfortunately, details of these risk factors and also age at first birth were not available. Menopausal status did not seem to account for the significant reduction in risk with increasing follow-up. There was no increased risk of invasive breast tumours. However there was a significant increase in in-situ tumours; significantly associated with increasing number of stimulated cycles. Interpretation of these findings is challenging: the significant association with increasing number of cycles is suggestive of an aetiological relationship, yet there was no overall increased risk of breast cancer. Other potential explanations include surveillance bias,

chance and potential confounding by factors such as socio-economic status, given that most cycles within our cohort were privately funded. To our knowledge this study is the first to analyse risks of in-situ and invasive breast cancers after assisted reproduction separately, so there are no previous data with which to compare.

Overall corpus uteri cancer risk was not raised. Women with the known risk factor of nulliparity[32] and those with a history of ovulatory problems (mainly the known risk factor polycystic ovary disease[33]) were found to have an increased risk. Most similar studies contained few events[3 5 6]. The largest included 15[4] and 49 cases[7], neither suggested an increased risk.

We found an excess of ovarian cancer compared with age-standardized expectation. Significant increases were observed for both invasive and borderline tumours, but were not seen in women without the known risk factors of endometriosis[34 35] and nulliparity[35]. Ovarian cancer risks were not associated with number of treatment cycles, time since treatment completion or male factor or unexplained infertility, which argues against a causal role for assisted reproduction procedures *per se*. However, we did find a significant association between age at first treatment and all ovarian cancer, invasive, and borderline tumour risk. Previous studies investigating invasive ovarian tumour risk after assisted reproduction [3-7 11 13 15 16] have generally found increased risks in comparison with the general population when potential confounding effects of infertility have not been considered[16], but not when such factors were taken into account[3 4 11 16]. Whilst our study compared cancer incidence with that in the general population (standardized for age and calendar year), it has sufficient size to stratify by potential confounding factors and thereby investigate characteristics of associations. We found an increased risk of borderline ovarian tumour in

women having assisted reproduction compared with the general population. As with invasive ovarian tumours, this increased risk was not seen in parous women without endometriosis. Few studies have investigated the risk of borderline ovarian cancer in women after assisted reproduction [6 13 14], but increased risks have been found in smaller studies in the Netherlands[13] and Australia[14]. While the increased risk could be genuine, it could also be due to surveillance bias. The frequency of borderline tumour diagnosis is increased in ovarian cancer screening studies using ultrasound[36] and women who have undergone assisted reproduction might have more frequent ultrasound scans post treatment than the general population. This is supported by the reduction in overall risk excluding the first 12 months follow-up. However, sensitivity analyses looking at time to diagnosis, age at diagnosis, diagnosis in women of high socio-economic status and clinical presentation in other studies suggested surveillance bias an unlikely cause of increased risks[13 14]. We are not able to further differentiate surveillance bias from a genuine increase in borderline tumours. Women with unrecorded cause of infertility had significantly increased rates of breast, ovarian and corpus uteri cancers. Reasons are unclear but might include reverse causality (*supplementary appendix*).

Strengths and Limitations

Most studies investigating risks of cancer in women after assisted reproduction have been small[6 8], with few events and short follow-up[4-7]. Two of the largest published to date include 67,608[4] and 113,226[7] women treated with assisted reproduction. Systematic reviews have included at most 70,753 treated women for analyses of breast cancer risk[10] and 79, 143 for ovarian cancer[16] and 118,32 for analysis of all gynaecological cancer risk[37] . Our study comprised over 250,000 treated women. We included almost 65,000 person-years follow up

for ≥15 years beyond last treatment with an average follow up of 8.8 years and a maximum follow-up of 19 years (*Table S2 supplementary appendix*), but cannot exclude the possibility of different risk profiles for any studied cancer on longer follow-up, at ages when most reproductive-related cancers occur[35]. Women treated with assisted reproduction are likely to differ from the general population in their parity, age at first birth, age at menopause, and the incidence of pre-disposing conditions, such as endometriosis. More information on these and others factors, such as socio-economic status, oral contraceptive use, body mass index, and breast-feeding would be useful. Comparison to women who have untreated infertility problems may have been beneficial, although interpretational problems would remain because of potential selection factors for treatment. Whilst our study was not able to compare with such a group as some smaller studies have done[4 13 14], large study size enabled us to stratify for some important potential confounders and draw inferences despite using general population rates as our comparator. Whilst comparator rates do include cohort participants, <5% of the population of reproductive-age women underwent assisted reproduction and our SIRs were generally <2.0; therefore resulting bias will have been minimal[38]. Infertility diagnoses were reported by treating fertility clinics to the HFEA. No data were available about how such diagnoses were made. Further details of specific treatments may have enabled detailed analysis of risk by treatment type. However over our 19 year study period, ovarian stimulation regimens as part of assisted reproductive cycles have been relatively constant, the majority of advances leading to better success rates having occurred in assisted reproduction laboratories. Gonadotropin injections have been used for ovarian stimulation and human chorionic gonadotropin for triggering ovulation throughout the study period, and whilst new highly purified and recombinant versions have been used in more recent years, they are essentially equivalent. Clomiphene citrate was

used as additional ovarian stimulation in the pioneering years of assisted reproduction treatment, but this was uncommon by 1991. Down-regulated cycles using GnRH-agonists were standard by 1991 and not replaced by GnRH antagonists as standard until after the study period. Progesterone support was used throughout the study period. The number of ovarian punctures per cycle and information about fertility treatment prior to assisted reproduction were not available.

Conclusions and Implications

In this large, national population-based study of British women after assisted reproductive technology treatment, no increased risk of corpus uteri or invasive breast cancer was detected. There was an increased risk of in-situ breast cancer associated with increasing number of treatment cycles. We also observed an excess of all types of ovarian cancer. However, our results suggest this is more likely due to underlying patient characteristics, rather than assisted reproduction *per se*. We were not able to distinguish between a genuine increase in borderline ovarian tumour risk and other explanations including surveillance bias. Further investigation of this and longer follow-up is warranted to continue monitoring these important outcomes in this ever-growing population.

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Dr Carrie Williams jointly conceptualized and designed the study, devised the linkage protocol, supervised the linkage, carried out the analysis, interpreted data, drafted the initial manuscript and approved the final manuscript as submitted. Dr Michael Jones jointly conceptualized and designed the study, jointly supervised the analysis, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Professor Anthony Swerdlow jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr Beverley Botting jointly conceptualized and designed the study, jointly supervised the analysis, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr Melanie Davies jointly conceptualized and designed the study,

interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Professor Ian Jacobs jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Mrs Kathryn Bunch jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr Michael Murphy jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Professor Alastair Sutcliffe jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and had the final decision over submission of the approved the final manuscript. All authors had access to the data and take responsibility for the integrity of the data and accuracy of the data analysis.

Professor Sutcliffe acts as guarantor for this study.

Transparency Declaration: Professor Sutcliffe affirms that the manuscript in an honest, accurate and transparent account of the study. No important aspects of the study have been omitted and any discrepancies from the study as planned have been explained.

Data Sharing Statement: No additional data are available, in compliance with ethical and governance regulations under which this research was undertaken.

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Table 1: Characteristics of 225,786 women who underwent assisted reproduction in Great Britain, 1991–2010

Characteristic	Total N=255, 786	Women who developed a cancer of the breast, ovary or corpus uteri N=3,155	Women who did not develop a cancer of the breast, ovary or corpus uteri N= 252,631
Mean age at first treatment- years (+/- Standard Deviation (SD))	34.5 +/- 4.8	36.3 +/- 4.7	34.5 +/- 4.8
Age at first treatment (years), No. (%)			
< 25	5,671 (2)	20 (1)	5,651 (2)
25-29	39,932 (16)	259 (8)	39,673 (16)
30- 34	92,788 (36)	961 (31)	91,827 (36)
35- 39	85,868 (34)	1,244 (39)	84,624 (34)
40-44	28,174 (11)	563 (18)	27,611 (11)
45+	3,353 (1)	108 (3)	3,245 (1)
Cause of infertility, No. (%)			
Any female factor	111,658 (44)	1,626 (52)	110,032 (44)
Male factor only	84,871 (33)	915 (29)	83,956 (33)
Unexplained	47,757 (19)	474 (15)	47,283 (19)
Unrecorded	11,500 (5)	140 (4)	11,360 (5)
History of endometriosis, No. (%)	18,630 (7)	281 (9)	18,349 (7)
History of tubal disease No. (%)	66,370 (26)	1045 (33)	65,325 (26)
History of ovulatory disorder, No. (%)	36,016 (14)	451 (14)	35,565 (14)
Mean duration of infertility reported at completion of last cycle Years +/- SD	4.9 +/- 3.3	5.6 +/- 3.9	4.8 +/- 3.3
Average number of stimulated cycles	1.8 +/-1.2	1.8 +/- 1.3	1.8 +/- 1.2
Average number of live births at completion of last cycle	0.6 +/- 0.7	0.6 +/- 0.7	0.6 +/- 0.7
Number of live births at completion of last cycle, No. (%)			
0	129,217 (51)	1,775 (56)	127,442 (50)
1	96,839 (38)	1,011 (32)	95,828 (38)
2+	29,645 (12)	368 (12)	29,277 (11)
Unrecorded	85 (0)	1 (0)	84 (0)
Any multiple birth recorded at completion of last cycle, No. (%)	29,366 (11)	304 (10)	29,062 (12)

Table 2: Relative and absolute excess risks of cancers of breast, ovary, and corpus uteri among 225,786 women who underwent assisted reproduction in Great Britain, 1991–2010, including and excluding the first year after the start of treatment.

Type of cancer	Person years follow-up	Observed cancers	Expected cancers	Standardized Incidence Ratio (95%CI)	AER[†] (95% CI)
Including the first year of follow-up					
Breast[‡]	2257789	2578	2641.2	0.98 (0.94-1.01)	-2.8 (-7.1 - 1.8)
Corpus uteri[§]	2257789	164	146.9	1.12 (0.95-1.30)	0.8 (-0.3 - 2.0)
Ovary[‖]	2257789	405	291.82	1.39 (1.26-1.53)***	5.0 (3.3 – 6.9)
Excluding the first year of follow-up					
Breast[‡]	2004121	2384	2501.6	0.95 (0.92-0.99)*	-5.9 (-10.6 - -1.0)
Corpus uteri[§]	2004121	157	141.79	1.11 (0.94-1.30)	0.8 (-0.4 - 2.1)
Ovary[‖]	2004121	356	271.9	1.31 (1.18-1.45)***	4.2 (2.44 – 6.10)

Table 3. Standardized incidence ratios for breast, ovarian and corpus uteri cancer among 225,786 women who underwent assisted reproduction in Great Britain, 1991–2010 stratified by various factors.

Factor	Type of Cancer[¶]					
	Breast[‡]		Corpus Uteri[§]		Ovarian[‖]	
	Observed cancers	SIR (95%CI)	Observed Cancers	SIR (95%CI)	Observed cancers	SIR (95%CI)
Age at first treatment (years)						
<25	14	1.32 (0.72-2.21)	0	0.00 (0.00-6.97)	6	2.21 (0.81-4.80)
25-29	185	0.92 (0.79-1.06)	10	1.24 (0.60-2.29)	64	2.16 (1.67-2.76)***
30-34	774	0.95 (0.89-1.02)	43	1.19 (0.86-1.60)	142	1.52 (1.28-1.80)***
35-39	1033	0.97 (0.91-1.03)	72	1.22 (0.96-1.54)	134	1.23 (1.03-1.45)*
40-44	479	1.02 (0.93-1.12)	33	0.96 (0.66-1.35)	50	1.05 (0.78-1.38)
45+	93	1.09 (0.89-1.34)	6	0.68 (0.25-1.48)	9	0.97 (0.45-1.85)
	Trend across categories P=0.13		Trend across categories P=0.28		Trend across categories P<0.001	
Infertility cause						
Any female factor	1279	0.95 (0.90-1.00)*	97	1.25 (1.02-1.53)*	246	1.66 (1.46-1.88)***
Male factor only	774	0.92 (0.86-0.99)*	41	0.91 (0.65-1.24)	98	1.05 (0.85-1.27)
Unexplained	416	1.10 (1.00-1.21)	16	0.78 (0.45-1.27)	40	0.96 (0.69-1.31)
Unrecorded	109	1.49 (1.24-1.80)***	10	2.53 (1.21-4.66)*	21	2.59 (1.60-3.95)**
History of endometriosis						
Yes	214	0.98 (0.86-1.12)	9	0.75 (0.35-1.43)	55	2.31 (1.74-3.01)***
No	2364	0.98 (0.94-1.02)	155	1.15 (0.98-1.34)	350	1.31 (1.17-1.45)***
History of tubal disease						
Yes	826	0.96 (0.90-1.03)	59	1.23 (0.93-1.58)	158	1.68 (1.43-1.97)***
No	1752	0.98 (0.94-1.03)	105	1.06 (0.87-1.29)	247	1.25 (1.10-1.41)***
History ovulatory problems						
Yes	357	0.92 (0.83-1.02)	39	1.59 (1.13-2.17)**	55	1.28 (0.97-1.67)
No	2221	0.99 (0.95-1.03)	125	1.02 (0.85-1.21)	350	1.41 (1.26-1.56)***

Duration of infertility at last cycle (years)						
< 2	171	0.95 (0.82-1.11)	6	0.55 (0.20-1.20)	28	1.44 (0.96-2.09)
2-3	527	1.05 (0.96-1.14)	23	0.82 (0.52-1.23)	73	1.30 (1.02-1.64)*
4-5	520	0.99 (0.90-1.07)	30	1.03 (0.70-1.47)	74	1.27 (1.00-1.60)
6-7	316	0.91 (0.82-1.02)	27	1.38 (0.91-2.01)	60	1.61 (1.23-2.07)**
8-9	197	0.95 (0.83-1.10)	16	1.34 (0.77-2.18)	36	1.64 (1.15-2.27)**
10+	322	0.95 (0.85-1.05)	37	1.68 (1.18-2.31)**	57	1.60 (1.21-2.08)**
Unrecorded	404	1.07 (0.97-1.18)	18	0.92 (0.54-1.45)	42	1.02 (0.74-1.38)
	Trend across categories P=0.20		Trend across categories P<0.001		Trend across categories P=0.15	
Total number of stimulated cycles						
0 – 'natural cycle' only	142	0.88 (0.74-1.04)	8	0.66 (0.28-1.29)	17	0.99 (0.58-1.59)
1	1203	0.98 (0.92-1.03)	89	1.29 (1.04-1.59)*	196	1.44 (1.25-1.66)***
2	585	1.01 (0.93-1.09)	29	0.91 (0.61-1.30)	87	1.38 (1.10-1.70)**
3-4	420	1.03 (0.93-1.13)	24	1.06 (0.68-1.58)	53	1.23 (0.92-1.60)
5+	107	1.08 (0.89-1.31)	7	1.24 (0.50-2.55)	17	1.67 (0.97-2.67)
Unrecorded	0	0 (0.00-29.96)	0	0.00 (0.00-13.03)	0	0.00 (0.00-299.57)
	Trend across categories P=0.07		Trend across categories P=0.93		Trend across categories P=0.86	
Total number of live births at last cycle completion						
0	1299	0.99 (0.93-1.04)	122	1.61 (1.34-1.92)***	222	1.57 (1.37-1.79)***
1	843	1.03 (0.96-1.10)	24	0.53 (0.34-0.79)***	114	1.25 (1.03-1.50)*
2+	314	0.92 (0.82-1.03)	11	0.54 (0.27-0.96)*	34	0.93 (0.64-1.30)
Unrecorded	1	1.82 (0.05-10.13)	0	0.00 (0.00-99.86)	0	0.00 (0.00-49.93)
	Trend across categories P=0.56		Trend across categories P<0.001		Trend across categories P=0.001	
Any multiple birth as recorded at last cycle completion						
Yes	258	1.10 (0.97-1.24)	5	0.42 (0.14-0.99)*	33	1.23 (0.85-1.73)
No	2199	0.98 (0.94-1.02)	152	1.17 (1.00-1.38)	337	1.39 (1.24-1.54)***

Time since last treatment (years)						
0-3	525	1.04 (0.95-1.13)	28	1.39 (0.92-2.00)	99	1.54 (1.25-1.88)***
3-6	529	1.04 (0.95-1.13)	29	1.28 (0.85-1.83)	73	1.27 (1.00-1.60)
6-10	657	1.00 (0.93-1.08)	38	1.07 (0.76-1.47)	84	1.24 (0.99-1.53)
10-15	590	0.93 (0.86-1.01)	45	0.99 (0.72-1.33)	86	1.39 (1.11-1.71)**
15+	156	0.86 (0.73-1.01)	17	0.98 (0.57-1.57)	28	1.57 (1.05-2.27)*
	Trend across categories P=0.01		Trend across categories P=0.12		Trend across categories P=0.74	

Table 4. Standardized incidence ratios for invasive and in-situ breast cancer and invasive and borderline tumours of the ovary among 255,786 women who underwent assisted reproduction in Great Britain, 1991-2010.

Factor[¶]	Invasive Breast Cancer[††]		In-situ Breast Cancer[‡‡]		Invasive Ovarian Tumours[§§]		Borderline Ovarian Tumors[‖‖]	
	Observed	SIR (95%CI)	Observed	SIR (95%CI)	Observed	SIR (95% CI)	Observed	SIR (95%CI)
Overall	2272	0.96 (0.92-1.00)*	291	1.15 (1.02-1.29)*	264	1.40 (1.24-1.58)***	141	1.36 (1.15-1.60)**
Age at first treatment (years)								
<25	14	1.43 (0.78-2.39)	0	0.00 (0.00-4.34)	<5	#	<5	#
25-29	168	0.91 (0.78-1.06)	16	1.10 (0.63-1.78)	35	2.33 (1.63-3.25)***	29	1.98 (1.33-2.85)**
30-34	685	0.92 (0.86-1.00)*	85	1.27 (1.02-1.57)*	81	1.46 (1.16-1.82)**	61	1.61 (1.23-2.07)**
35-39	925	0.97 (0.91-1.04)	100	0.94 (0.77-1.15)	97	1.32 (1.07-1.61)*	37	1.04 (0.73-1.43)
40-44	411	1.00 0.90-1.10)	66	1.23 (0.95-1.56)	40	1.13 (0.80-1.53)	10	0.82 (0.39-1.50)
45+	69	0.94 (0.73-1.19)	24	2.12 (1.36-3.15)**	<10	#	<5	#
	Trend across categories P=0.30		Trend across categories P=0.47		Trend across categories P=0.02		Trend across categories P<0.001	
Infertility cause								
Any female factor	1118	0.92 (0.87-0.98)**	151	1.14 (0.97-1.34)	161	1.66 (1.41-1.94)***	85	1.66 (1.33-2.05)***
Male factor only	676	0.89 (0.83-0.96)**	93	1.18 (0.95-1.44)	65	1.09 (0.84-1.39)	33	0.96 (0.66-1.35)
Unexplained	374	1.10 (0.99-1.22)	42	1.18 (0.85-1.59)	26	0.98 (0.64-1.44)	14	0.92 (0.50-1.55)
Unrecorded	104	1.58 (1.30-1.92)***	5	0.73 (0.24-1.70)	12	2.35 (1.21-4.10)*	9	3.00 (1.37-5.70)*
History of endometriosis								
Yes	186	0.95 (0.82-1.10)	26	1.25 (0.81-1.83)	38	2.47 (1.75-3.39)***	17	2.03 (1.18-3.25)*
No	2086	0.96 (0.92-1.00)	265	1.14 (1.01-1.28)*	226	1.31 (1.14-1.49)***	124	1.30 (1.08-1.55)**
History of tubal disease								
Yes	725	0.94 (0.87-1.01)	92	1.11 (0.89-1.36)	105	1.71 (1.40-2.08)***	53	1.62 (1.21-2.12)*
No	1547	0.97 (0.92-1.01)	199	1.17 (1.01-1.34)*	159	1.25 (1.07-1.46)**	88	1.24 (0.99-1.53)
History of ovulatory problems								
Yes	315	0.91 (0.81-1.02)	41	1.05 (0.75-1.42)	33	1.16 (0.80-1.63)	22	1.52 (0.96-2.31)
No	1957	0.97 (0.92-1.01)	250	1.17 (1.03-1.32)*	231	1.45 (1.27-1.65)***	119	1.33 (1.11-1.60)**
Duration of infertility at last cycle (years)								

< 2	156	0.97 (0.83-1.14)	15	0.82 (0.46-1.35)	16	1.23 (0.70-1.99)	12	1.89 (0.98-3.30)
2-3	464	1.03 (0.94-1.13)	61	1.26 (0.97-1.62)	53	1.48 (1.11-1.93)*	20	0.99 (0.61-1.53)
4-5	461	0.97 (0.89-1.07)	52	1.03 (0.77-1.35)	53	1.42 (1.06-1.85)*	21	1.02 (0.63-1.55)
6-7	278	0.90 (0.79-1.01)	35	1.03 (0.72-1.44)	40	1.63 (1.16-2.21)**	20	1.57 (0.96-2.42)
8-9	169	0.92 (0.78-1.06)	27	1.31 (0.86-1.91)	27	1.84 (1.21-2.67)**	9	1.24 (0.57-2.36)
10+	279	0.92 (0.82-1.04)	42	1.15 (0.83-1.56)	40	1.60 (1.14-2.18)**	17	1.61 (0.94-2.58)
Unrecorded	355	1.05 (0.94-1.16)	48	1.37 (1.01-1.82)*	25	0.97 (0.63-1.43)	17	1.12 (0.65-1.79)
	Trend across categories P=0.11		Trend across categories P=0.58		Trend across categories P=0.25		Trend across categories P=0.42	
Total number of stimulated cycles								
0 – 'natural cycle' only	121	0.85 (0.71-1.02)	21	1.14 (0.71-1.74)	13	1.04 (0.55-1.78)	<5	#
1	1073	0.97 (0.91-1.03)	121	1.02 (0.85-1.22)	129	1.47 (1.23-1.75)***	67	1.39 (1.08-1.77)*
2	512	0.98 (0.90-1.07)	70	1.25 (0.97-1.58)	56	1.37 (1.03-1.78)*	31	1.40 (0.95-1.98)
3-4	371	1.01 (0.92-1.12)	47	1.18 (0.87-1.57)	42	1.48 (1.06-1.99)*	11	0.75 (0.37-1.33)
5+	85	0.96 (0.77-1.91)	21	2.11 (1.31-3.23)**	14	2.04 (1.11-3.42)*	<5	#
	Trend across categories P=0.27		Trend across categories P=0.03*		Trend across categories P=0.29		Trend across categories P=0.18	
Total number of live births after last treatment								
0	1154	0.98 (0.92-1.04)	135	1.04 (0.87-1.23)	156	1.67 (1.42-1.95)***	66	1.38 (1.07-1.75)*
1	732	0.99 (0.92-1.07)	107	1.37 (1.12-1.65)**	78	1.34 (1.06-1.67)*	36	1.09 (0.76-1.51)
2+	276	0.90 (0.80-1.02)	37	1.07 (0.76-1.48)	20	0.81 (0.50-1.26)	14	1.16 (0.63-1.95)
Unrecorded	0	0.00	1	20.00 (0.51-111.43)	0	0.00 (0.00-74.89)	0	0.0 (0.0-149.79)
	Trend across categories P=0.37		Trend across categories P=0.32		Trend across categories P=0.001		Trend across categories P=0.34	
Any multiple birth recorded								
Yes	234	1.10 (0.97-1.25)	22	1.05 (0.66-1.58)	22	1.34 (0.84-2.03)	11	1.06 (0.53-1.90)
No	1928	0.96 (0.92-1.00)	258	1.16 (1.02-1.31)*	232	1.45 (1.27-1.65)***	105	1.27 (1.04-1.54)*
Time since last treatment (years)								
0-3	488	1.05 (0.96-1.15)	37	1.06 (0.71-1.39)	62	1.73 (1.33-2.22)***	37	1.30 (0.92-1.79)
3-6	476	1.03 (0.94-1.12)	51	1.24 (0.93-1.63)	45	1.27 (0.93-1.71)	28	1.27 (0.85-1.84)
6-10	556	0.94 (0.87-1.02)	95	1.52 (1.23-1.85)***	63	1.37 (1.05-1.75)*	21	0.96 (0.59-1.46)
10+	510	0.93 (0.85-1.01)	75	0.98 (0.77-1.22)	63	1.38 (1.06-1.77)*	23	1.39 (0.88-2.08)
15+	132	0.86 (0.72-1.02)	22	0.85 (0.54-1.29)	21	1.52 (0.94-2.32)	7	1.75 (0.70-3.60)
	Trend across categories P=0.005**		Trend across categories P=0.29		Trend across categories P=0.44		Trend across categories P=0.84	

Table 5. Standardized incidence ratios for all ovarian cancers, invasive and borderline ovarian tumours among 225,786 women who underwent assisted reproduction in Great Britain, 1991–2010, by presence or absence of known risk factors endometriosis and nulliparity.

Factor	Type of ovarian cancer					
	All ovarian cancer[‖]		Invasive cancer[§§]		Borderline tumours[‖‖]	
	Observed Cancers	SIR (95%CI)	Observed cancers	SIR (95%CI)	Observed cancers	SIR (95%CI)
No diagnosis of endometriosis and at least one birth recorded by treatment completion	133	1.03 (0.86-1.22)	85	1.03 (0.82-1.27)	48	1.02 (0.75-1.35)
No diagnosis of endometriosis and no births recorded by treatment completion	217	1.57 (1.37-1.79)***	141	1.56 (1.32-1.84)***	76	1.57 (1.24-1.97)***
Diagnosis of endometriosis and at least one birth recorded by treatment completion	24	2.41 (1.55-3.59)***	14	2.22 (1.21-3.72)*	10	2.76 (1.33-5.08)*
Diagnosis of endometriosis and no birth recorded by treatment completion	31	2.24 (1.52-3.18)***	24	2.64 (1.69-3.93)***	7	1.47 (0.59-3.04)

Table Legends

† Absolute Excess Risk per 100,000 person years at risk

‡ 'Breast Cancer'= ICD-9: 1740-9, 2330, 2383; ICD-10: C500-9, D050-9, D486

§ 'Corpus Uteri Cancer'= ICD-9: 1820-8; ICD-10: C54

‖ 'Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, D391

*P<0.05 **P<0.01 ***P<0.001

¶ See Supplemental Data for results excluding the first 12 months of follow up.

†† 'Invasive Breast Cancer'= ICD-9: 1740-9: ICD-10:C500-9

‡‡ 'In-situ Breast Cancer'= ICD-9: 2330: ICD-10: D050-9

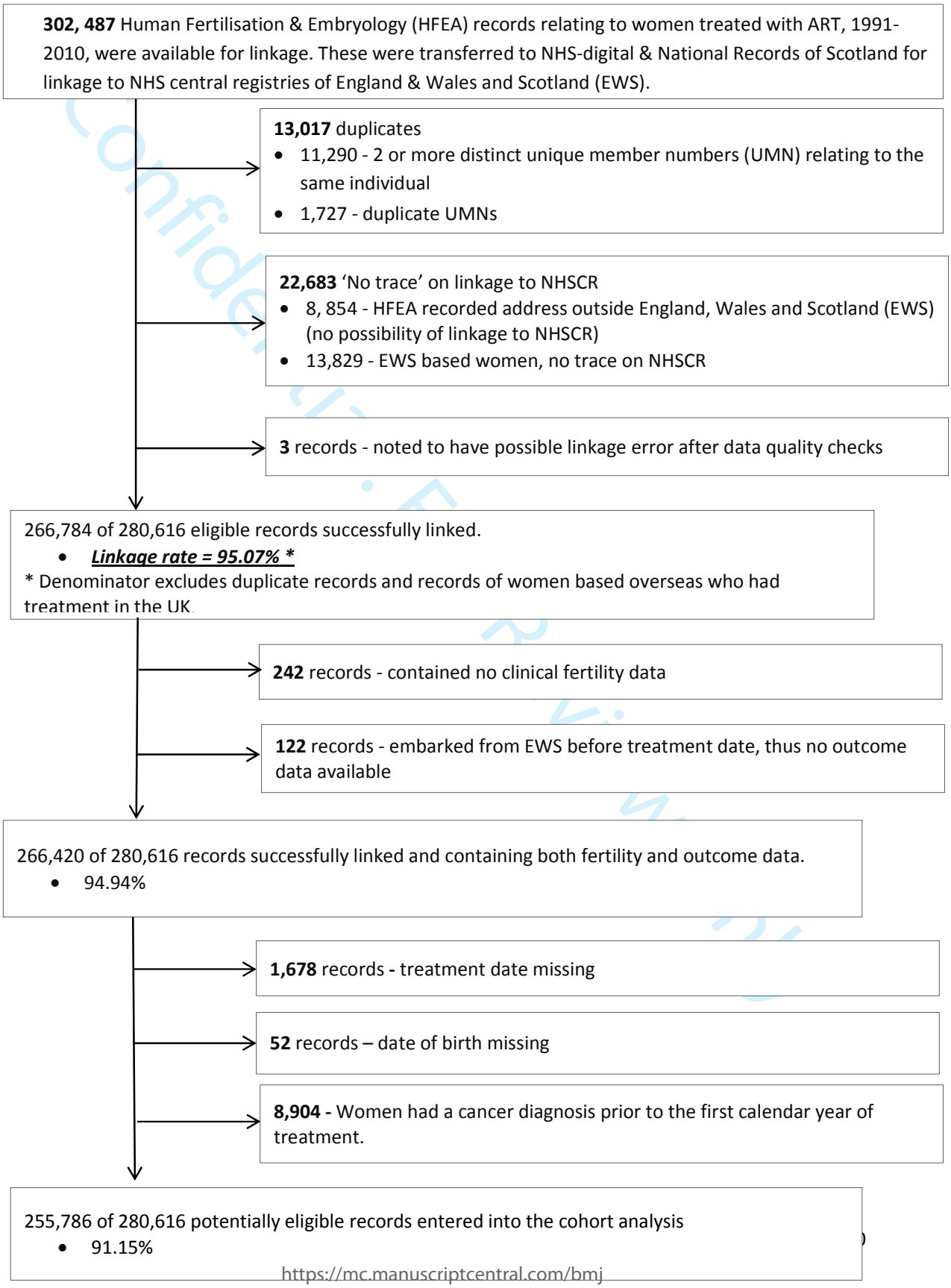
§§ 'Invasive Ovarian Tumours'= ICD-9: 1830-1839 (excluding morphology codes 8442/8451/8462/8472/8473) 2362; ICD-10: C56, C570-C574, C481, C482 (excluding morphology codes 8442/8451/8462/8472/8473).

‖‖ 'Borderline Ovarian Tumours'=ICD-9 1830 (with morphology codes 8442/8451/8462/8472/8473); ICD-10 D391, C56 (with morphology codes 8442/8451/8462/8472/8473).

SIRs suppressed to comply with data disclosure regulations where cells relate to small numbers of individuals. None of the SIRs for affected cells approached significance.

Suggested supplementary appendix

Figure S1- Flow diagram of cohort records



Box S1- Details of linkage & analysis

Details of linkage at National Health Service-Digital and National Records for Scotland

Matching was initially deterministic, matching on:-

- Forename, Surname
- 2 of 3 parts of date of birth match

If more than one match was found no match was accepted and the records would go for manual matching along with unmatched records. Manual matching utilised: -

- Forename, Surname, Date of birth
- Other recorded names
- Place of birth
- Treatment centre/ Cycle date

Quality control process: -

Automatic matching algorithm used (A) was tested against an algorithm using exact date of birth match (B). Both A and B were performed on 4239 cases. The 4239 cases then underwent manual matching gold standard.

A – 0/4239 false positive matches

B – 9/4239 false positive matches

Additional details of analysis: -

As detailed in the main paper, expected cancers were calculated by multiplying person-years at risk by corresponding national incidence rates (by 5-year age band and individual calendar year) for the general population of England & Wales. Annual national incidence rates 1991-1998 are for England and Wales, thereafter national rates refer to England only as rates were not published for England and Wales.

Table S1. Meta-data for available HFEA variables (linked cohort)

HFEA data item	Frequency	Details	Data Source	% complete
Date of Birth	255,786		Self-reported to HFEA	100
Ethnic group	46,107	30 potential responses	Self-reported to HFEA	18.0
Start date of first treatment cycle	255,786	Year of each treatment cycle recorded. Year mid-point used to calculate person-years at risk.	Clinic reported to HFEA	100
Start date of last treatment cycle	255,786		Clinic reported to HFEA	100
Age at first treatment	255,786	Categorised: - <25 yrs- 5,671 25-29 yrs- 39,932 30-34 yrs- 92,788 35-39 yrs- 85,868 40-44 yrs- 28,174 45+yrs – 3,353	Derived, first treatment cycle date minus date of birth	100
Broad Cause of infertility	244,286	Female- 70,293 Male- 84,871 Both- 41,365 Unexplained- 47,757 Unrecorded- 11,500 & all specific causes negative.	Clinic reported to HFEA	95.5
Endometriosis	255,786	Yes- 18,630 No- 237,156	Clinic reported to HFEA	100
Tubal disease	255,786	Yes- 66,370 No- 189,416	Clinic reported to HFEA	100
Ovulatory disorder	255,786	Yes- 36,016 No- 219,770	Clinic reported to HFEA	100
Male factor infertility	255,786	Any Yes-126,236 No-129,550 Sperm concentration Yes- 18,679 No-237,107 Sperm morphology Yes-10,586 No-245,200 Sperm motility Yes-9,263 No-246,523 Sperm immune issue Yes-2,493 No-253,293	Clinic reported to HFEA	
Primary Female infertility	255,576	Yes-113,918 No- 141,658 Unrecorded-210	Clinic reported to HFEA	99.9
Secondary Female Infertility	255,786	Yes-86,322 No-169,464	Clinic reported to HFEA	100
Primary Male Infertility	255,786	Yes-117,207 No-138,579	Clinic reported to HFEA	100
Secondary Male Infertility	255,786	Yes-80,843 No-174,943	Clinic reported to HFEA	100
Primary Couple infertility	255,786	Yes-139,272 No-116,514	Clinic reported to HFEA	100
Secondary Couple infertility	255,786	Yes-58,584 No-197,202	Clinic reported to HFEA	100
Duration of infertility	206,304	<2yrs- 17,194 2-3yrs- 67,529 4-5yrs- 56,203 6-7yrs- 29,946 8-9yrs - 15,394 >=10yrs -20,038 Unrecorded- 49,482	Self-reported to HFEA	80.6

Number of Treatment cycles	255,778	Natural cycle only-9,781 Stimulated cycles- 1- 131,670 2- 63,842 3-4- 41,224 5+ - 9,261 Unrecorded - 8	Clinic reported to HFEA	99.9
Type of ART treatment	255,177	IVF only- 150,700 ICSI/ Unspecified micromanipulation- 76, 596 IVF & ICSI- 27,881	Clinic reported to HFEA	99.8
Treatment centre	255,786	Treatment centre only geographical variable available	Clinic reported to HFEA	100
Number of Pregnancies by end of last treatment cycle	255,377	0- 82,747 1- 94,836 2-3- 63,821 4-5- 11,246 6+ 2,727 Unknown - 409	Derived variable from self - reported pregnancies on registration of last treatment cycle plus HFEA recorded ART pregnancies from last treatment cycle (validated against HFEA recorded ART pregnancies from previous cycles).	99.8
Years since last pregnancy	121,698	Variable contains a number of values which are likely to be age at last pregnancy.	Self-reported to HFEA	47.6
Age at last pregnancy	121,698	Median- 31.7 yrs IQR 35.5-27.7 yrs	Self-reported to HFEA	47.6
Number of live births by end of last treatment cycle	255,701	0- 129,217 1- 96,839 2-3- 27,593 4+ 2,052 Unrecorded- 85	Derived variable from self - reported births on registration of last treatment cycle plus HFEA recorded ART birth from last treatment cycle (validated against HFEA recorded ART births from previous cycles).	99.9
Multiple births	255,786	Yes- 29,366 No- 29,366	Clinic reported to HFEA	100
ART birth recorded by HFEA	255,786	Yes- 105,183 No-150,183	Clinic reported to HFEA	100

Figure S2- Person years of follow up within the cohort of women who had assisted conception, by year of first treatment

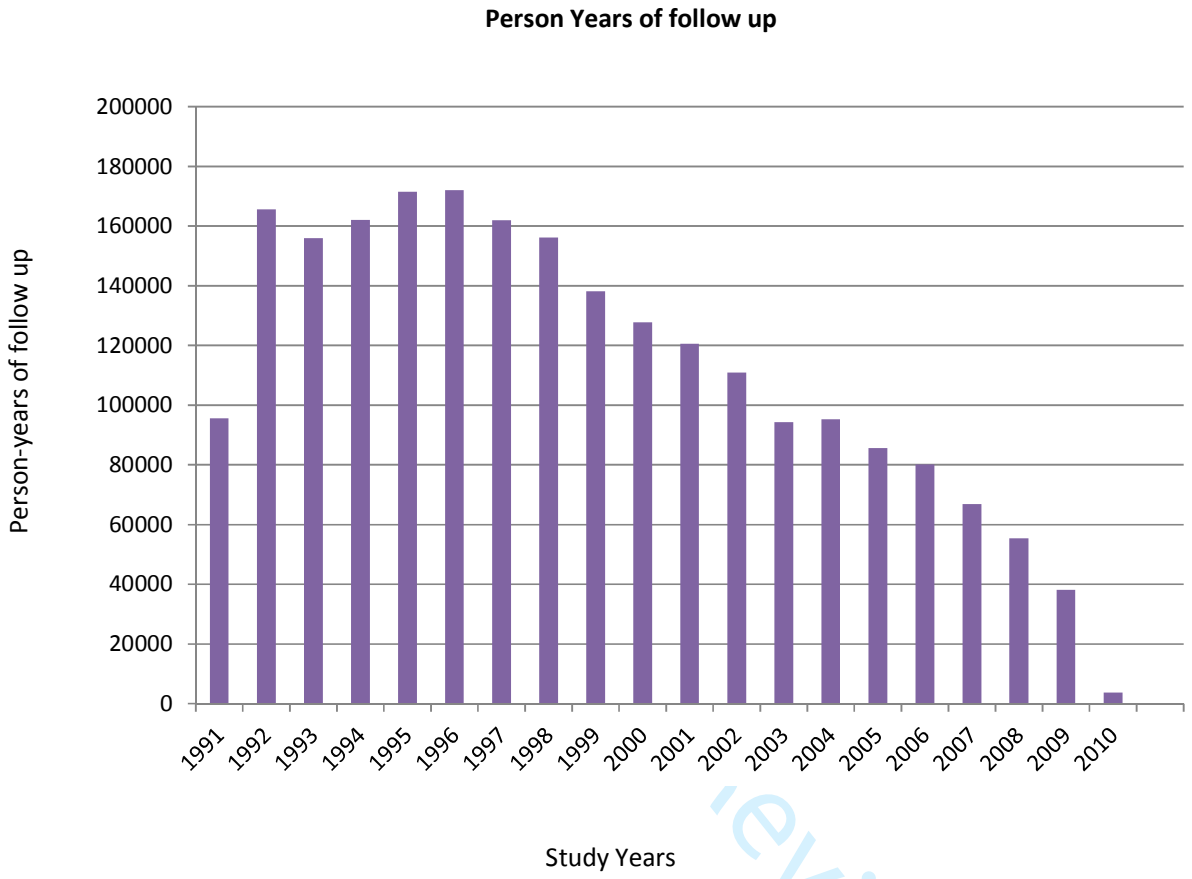


Table S2- Cohort frequency and person years of follow up by year of first

Year of first treatment	No. of women	%	Cumulative %	Person-years of follow-up	Person-years as % of total	Cumulative person years as % of cohort
1991	5,047	2.0	1.97	95654	4.2	4.2
1992	9,169	3.6	5.56	165557	7.3	11.6
1993	9,095	3.6	9.11	155957	6.9	18.5
1994	9,996	3.9	13.02	162009	7.2	25.7
1995	11,216	4.4	17.41	171479	7.6	33.3
1996	12,004	4.7	22.10	172036	7.6	40.9
1997	12,124	4.7	26.84	161905	7.2	48.1
1998	12,578	4.9	31.76	156201	6.9	55.0
1999	12,058	4.7	36.47	138110	6.1	61.1
2000	12,149	4.8	41.22	127788	5.7	66.8
2001	12,622	4.9	46.15	120568	5.3	72.1
2002	12,932	5.1	51.21	110950	4.9	77.0
2003	12,414	4.9	56.06	94329	4.2	81.2
2004	14,368	5.6	61.68	95264	4.2	85.4
2005	15,144	5.9	67.60	85673	3.8	89.2
2006	17,130	6.7	74.30	80136	3.6	92.7
2007	18,070	7.1	81.36	66809	3.0	95.7
2008	20,494	8.0	89.38	55464	2.5	98.2
2009	22,068	8.6	98.00	38141	1.7	99.9
2010	5,108	2.0	100.00	3760	0.2	100.0
Total	255,786	100.0	100.00	2257789	100.0	100.0

Table S3- Sensitivity analysis excluding the first 12 months of follow up for breast, corpus uteri and ovarian cancer

Factor	Type of Cancer					
	Breast‡		Corpus Uteri§		Ovarian‖	
	Observed Cancers	SIR (95%CI)	Observed Cancers	SIR (95%CI)	Observed Cancers	SIR (95%CI)
Overall	2384	0.95 (0.92-0.99)*	157	1.12 (0.94-1.30)	356	1.31 (1.18-1.45)***
Age at first treatment (years)						
<25	11	1.05 (0.53-1.88)	0	0.00 (0.00-7.13)	<5	#
25-29	171	0.87 (0.74-1.01)	8	1.01 (0.44-2.00)	55	1.99 (1.50-2.59)***
30-34	723	0.92 (0.86-0.99)*	41	1.16 (0.83-1.58)	124	1.42 (1.18-1.69)***
35-39	955	0.95 (0.89-1.02)	70	1.23 (0.96-1.55)	118	1.16 (0.96-1.39)
40-44	436	1.01 (0.92-1.11)	32	0.97 (0.67-1.37)	47	1.07 (0.78-1.42)
45+	88	1.13 (0.91-1.39)	6	0.71 (0.26-1.56)	<10	#
	Trend across categories P=0.03		Trend across categories P=0.54		Trend across categories P=0.001	
Infertility cause						
Any female factor	1224	0.95 (0.90-1.00)	95	1.26 (1.02-1.54)*	221	1.58 (1.38-1.81)***
Male factor only	727	0.91 (0.85-0.98)**	40	0.92 (0.66-1.25)	88	1.01 (0.81-1.24)
Unexplained	377	1.08 (0.98-1.20)	16	0.83 (0.47-1.35)	33	0.88 (0.60-1.23)
Unrecorded	56	0.87 (0.66-1.13)	6	1.67 (0.61-3.64)	14	1.98 (1.08-3.33)*
History of endometriosis						
Yes	204	0.98 (0.85-1.12)	9	0.78 (0.35-1.47)	49	2.19 (1.62-2.89)***
No	2180	0.95 (0.91-0.99)*	148	1.14 (0.96-1.34)	307	1.23 (1.10-1.38)**
History of tubal disease						
Yes	800	0.97 (0.90-1.04)	57	1.21 (0.92-1.57)	151	1.69 (1.44-1.99)***
No	1584	0.95 (0.90-0.99)*	100	1.06 (0.86-1.28)	205	1.12 (0.97-1.29)
History of ovulatory problems						
Yes	333	0.91 (0.82-1.02)	38	1.65 (1.17-2.27)**	43	1.08 (0.78-1.45)
No	2051	0.96 (0.92-1.00)	119	1.00 (0.83-1.20)	313	1.35 (1.20-1.51)***
Duration of infertility at last treatment cycle (years)						
< 2	142	0.84 (0.71-1.00)	<5	## *	23	1.26 (0.82-1.93)
2-3	481	1.04 (0.95-1.14)	22	0.83 (0.52-1.26)	62	1.23 (0.94-1.57)
4-5	498	1.00 (0.92-1.10)	30	1.07 (0.73-1.54)	66	1.23 (0.95-1.57)
6-7	298	0.91 (0.81-1.02)	27	1.43 (0.94-2.07)	57	1.63 (1.24-2.12)**
8-9	185	0.94 (0.81-1.08)	16	1.38 (0.79-2.24)	33	1.60 (1.10-2.24)†
10+	305	0.94	37	1.72	50	1.49

		(0.84-1.05)		(1.21-2.38)**		(1.10-1.96)†
Unrecorded	360	1.06 (0.95-1.17)	<20	#	36	0.99 (0.69-1.37)
	Trend across categories P=0.47		Trend across categories P<0.001		Trend across categories P=0.13	
Total number of stimulated cycles						
0 – 'natural cycle' only	136	0.90 (0.76-1.07)	8	0.68 (0.30-1.35)	15	0.94 (0.53-1.55)
1	1107	0.96 (0.90-1.01)	85	1.29 (1.03-1.59)*	174	1.39 (1.19-1.61)***
2	545	1.01 (0.93-1.10)	29	0.95 (0.64-1.37)	77	1.33 (1.05-1.67)*
3-4	381	1.01 (0.91-1.11)	24	1.12 (0.72-1.66)	48	1.22 (0.90-1.61)
5+	100	1.10 (0.90-1.34)	5	0.94 (0.31-2.19)	13	1.41 (0.75-2.41)
Unrecorded	0	0.00 (0.00-33.29)	0	0.00 (0.00-299.57)	0	0.00 (0.00-299.57)
	Trend across categories P=0.13		Trend across categories P=0.81		Trend across categories P=0.95	
Total number of live births at last cycle completion						
0	1166	0.95 (0.89-1.00)	116	1.60 (1.32-1.92)***	189	1.45 (1.25-1.67)***
1	801	1.04 (0.97-1.12)	24	0.56 (0.36-0.83)**	109	1.31 (1.07-1.58)**
2+	301	0.94 (0.84-1.05)	11	0.56 (0.28-1.00)*	29	0.86 (0.57-1.23)
Unrecorded	1	2.13 (0.05-11.86)	0	0.00 (0.00-99.86)	0	0.00 (0.00-59.92)
	Trend across categories P=0.48		Trend across categories P<0.001		Trend across categories P=0.01	
Multiple birth as recorded at last cycle completion						
Yes	253	1.15 (1.01-1.30)*	5	0.44 (0.14-1.03)*	31	1.26 (0.86-1.79)
No	2016	0.96 (0.92-1.00)	146	1.18 (1.00-1.39)	296	1.33 (1.18-1.49)***
Time since last treatment (years)						
0-3	337	0.99 (0.88-1.10)	22	1.58 (0.99-2.39)	56	1.32 (1.00-1.71)
3-6	529	1.04 (0.95-1.13)	29	1.28 (0.85-1.83)	73	1.27 (1.00-1.60)
6-10	657	1.00 (0.93-1.08)	38	1.07 (0.76-1.47)	84	1.24 (0.99-1.53)
10-15	590	0.93 (0.86-1.01)	45	0.99 (0.72-1.33)	86	1.39 (1.11-1.71)**
15+	156	0.86 (0.73-1.01)	17	0.98 (0.57-1.57)	28	1.57 (1.04-2.27)*
	Trend across categories P=0.06		Trend across categories P=0.06		Trend across categories P=0.46	

Table S4- Sensitivity analysis excluding the first 12 months of follow up for invasive and borderline ovarian tumours

Factor	Invasive Ovarian Tumours[§§]		Borderline Ovarian Tumors[‖‖]	
	Observed Cancers	SIR (95%CI)	Observed Cancers	SIR (95%CI)
Overall	244	1.37 (1.21-1.56)***	112	1.19 (0.98-1.43)
Age at first treatment (years)				
<25	<5	#	<5	#
25-29	32	2.24 (1.53-3.16)***	23	1.72 (1.09-2.58)*
30-34	76	1.44 (1.13-1.80)**	48	1.39 (1.02-1.84)*
35-39	87	1.25 (1.01-1.55)*	31	0.96 (0.65-1.37)
40-44	39	1.17 (0.83-1.60)	8	0.74 (0.32-1.46)
45+	<10	#	<5	#
	Trend across categories P=0.01		Trend across categories P=0.01	
Infertility cause				
Any female factor	155	1.67 (1.42-1.96)***	66	1.40 (1.09-1.79)*
Male factor only	60	1.06 (0.81-1.37)	28	0.90 (0.60-1.30)
Unexplained	20	0.82 (0.50-1.27)	13	0.98 (0.52-1.67)
Unrecorded	9	1.99 (0.91-3.78)	5	1.98 (0.64-4.61)
History of endometriosis				
Yes	37	2.51 (1.77-3.47)***	12	1.57 (0.81-2.73)
No	207	1.27 (1.10-1.45)**	100	1.16 (0.94-1.41)
History of tubal disease				
Yes	101	1.72 (1.40-2.09)***	50	1.65 (1.23-2.18)**
No	143	1.20 (1.01-1.42)*	62	0.97 (0.75-1.25)
History of ovulatory problems				
Yes	32	1.19 (0.82-1.61)	11	0.84 (0.42-1.51)
No	212	1.40 (1.22-1.61)***	101	1.25 (1.02-1.52)*
Duration of infertility at last treatment cycle (years)				
< 2	15	1.23 (0.69-2.02)	8	1.41 (0.61-2.79)
2-3	47	1.43 (1.05-1.90)*	15	0.85 (0.48-1.41)
4-5	49	1.40 (1.03-1.85)*	17	0.92 (0.54-1.47)
6-7	39	1.67 (1.19-2.29)**	18	1.55 (0.92-2.45)
8-9	25	1.78 (1.15-2.63)*	8	1.21 (0.52-2.37)
10+	35	1.46 (1.02-2.03)*	15	1.55 (0.87-2.55)
Unrecorded	21	0.90 (0.56-1.38)	15	1.13 (0.63-1.87)
	Trend across categories P=0.39		Trend across categories P=0.17	

Total number of stimulated cycles				
0 – 'natural cycle' only	13	1.11 (0.59-1.90)	<5	#
1	118	1.43 (1.19-1.72)***	56	1.30 (0.98-1.69)
2	50	1.32 (0.98-1.73)	27	1.37 (0.90-1.99)
3-4	39	1.48 (1.05-2.02)*	9	0.69 (0.32-1.31)
5+	11	1.74 (0.87-3.11)	<5	#
		Trend across categories P=0.48		Trend across categories P=0.30
Total number of live births at last cycle completion				
0	136	1.55 (1.30-1.84)***	53	1.24 (0.93-1.62)
1	77	1.42 (1.12-1.78)**	32	1.09 (0.75-1.54)
2+	18	0.78 (0.46-1.23)	11	1.01 (0.51-1.81)
Unrecorded	0	0.00 (0.00-99.86)	0	0.00 (0.00-149.8)
		Trend across categories P=0.01		Trend across categories P=0.46
Multiple birth as recorded at last cycle completion				
Yes	21	1.37 (0.85-2.09)	10	1.08 (0.52-1.99)
No	210	1.41 (1.22-1.61)***	86	1.17 (0.93-1.44)
Time since last treatment (years)				
0-3	39	1.62 (1.15-2.21)**	17	0.93 (0.54-1.48)
3-6	45	1.27 (0.93-1.71)	28	1.27 (0.85-1.84)
6-10	63	1.37 (1.05-1.75)*	21	0.96 (0.59-1.46)
10-15	63	1.38 (1.06-1.77)*	23	1.39 (0.88-2.08)
15+	21	1.52 (0.94-2.32)	7	1.75 (0.70-3.60)
		Trend across categories P=0.85		Trend across categories P=0.21

Table S5- Sensitivity analysis excluding the first 12 months of follow up for invasive and in-situ breast cancer

Factor	Invasive breast cancer††		In situ- breast cancer‡‡	
	Obs. Cancers	SIR (95%CI)	Obs. Cancers	SIR (95%CI)
Overall	2089	0.93 (0.89-0.97)**	280	1.15 (1.02-1.29)*
Age at first treatment (years)				
<25	11	1.14 (0.57-2.04)	0	0.00 (0.00-4.41)
25-29	154	0.85 (0.72-1.00)*	16	1.12 (0.64-1.81)
30-34	635	0.89 (0.82-0.96)**	84	1.29 (1.03-1.59)*
35-39	850	0.95 (0.89-1.02)	97	0.95 (0.77-1.16)
40-44	373	0.99 (0.89-1.09)	61	1.19 (0.91-1.53)
45+	66	0.99 (0.76-1.26)	22	2.06 (1.29-3.12)**
	Trend across categories P=0.07		Trend across categories P=0.67	
Infertility cause				
Any female factor	1068	0.93 (0.87-0.98)**	146	1.14 (0.96-1.34)
Male factor only	632	0.88 (0.81-0.95)**	90	1.18 (0.95-1.45)
Unexplained	337	1.08 (0.97-1.20)	<45	#
Unrecorded	52	0.90 (0.67-1.18)	<5	#
History of endometriosis				
Yes	176	0.94 (0.81-1.09)	26	1.28 (0.84-1.88)
No	1913	0.93 (0.89-0.97)**	254	1.13 (1.00-1.28)
History of tubal disease				
Yes	701	0.95 (0.88-1.02)	90	1.11 (0.89-1.36)
No	1388	0.92 (0.87-0.97)**	190	1.17 (1.01-1.34)*
History of ovulatory problems				
Yes	294	0.90 (0.80-1.01)	38	1.01 (0.72-1.39)
No	1795	0.94 (0.89-0.98)**	242	1.17 (1.03-1.33)*
Duration of infertility at last treatment cycle (years)				
< 2	128	0.85 (0.71-1.02)	14	0.80 (0.44-1.34)
2-3	422	1.02 (0.92-1.12)	57	1.25 (0.95-1.63)
4-5	439	0.99 (0.90-1.08)	52	1.08 (0.80-1.41)
6-7	260	0.88 (0.78-1.00)*	35	1.07 (0.75-1.49)
8-9	159	0.90 (0.77-1.06)	25	1.25 (0.81-1.85)
10+	262	0.91 (0.80-1.03)	42	1.19 (0.86-1.60)
Unrecorded	311	1.02 (0.91-1.14)	48	1.49 (1.10-1.97)*
	Trend across categories P=0.30		Trend across categories P=0.53	

Total number of stimulated cycles				
0 – 'natural cycle' only	115	0.87 (0.72-1.04)	21	1.20 (0.74-1.83)
1	981	0.95 (0.89-1.01)	117	1.03 (0.85-1.23)
2	472	0.97 (0.89-1.07)	70	1.32 (1.03-1.66)*
3-4	334	0.99 (0.88-1.10)	45	1.19 (0.87-1.60)
5+	79	0.98 (0.77-1.22)	20	2.14 (1.31-3.31)**
Unrecorded	0	0.00 (0.00-37.45)	0	0.00 (0.00-299.57)
	Trend across categories P=0.27		Trend across categories P=0.03*	
Total number of live births at last cycle completion				
0	1027	0.94 (0.88-0.99)*	129	1.04 (0.87-1.23)
1	691	1.00 (0.93-1.08)	106	1.43 (1.17-1.72)**
2+	263	0.92 (0.81-1.04)	37	1.12 (0.79-1.55)
Unrecorded	0	0.00 (0.00-7.13)	1	20.00 (0.51-111.43)
	Trend across categories P=0.71		Trend across categories P=0.21	
Any multiple birth as recorded at last cycle completion				
Yes	230	1.16 (1.01-1.32)*	21	1.04 (0.65-1.59)
No	1751	0.93 (0.89-0.98)**	252	1.19 (1.05-1.35)**
Time since last treatment (years)				
0-3	307	0.98 (0.87-1.09)	30	1.18 (0.80-1.69)
3-6	476	1.03 (0.94-1.12)	51	1.24 (0.93-1.63)
6-10	556	0.94 (0.87-1.02)	95	1.52 (1.23-1.85)***
10-15	510	0.93 (0.85-1.01)	75	0.98 (0.77-1.22)
15+	132	0.86 (0.72-1.02)	22	0.85 (0.54-1.29)
	Trend across categories P=0.07		Trend across categories P=0.07	

Table S6- Risk of any ovarian cancer, invasive and borderline ovarian tumours in women with and without endometriosis and or nulliparity, stratified by age at first treatment

Factor	Type of ovarian tumour					
	All ovarian tumours[‖]		Invasive ovarian tumour[§§]		Borderline ovarian tumour[‖‖]	
	Observed Cancers	SIR (95%CI)	Observed Cancers	SIR (95%CI)	Observed Cancers	SIR (95%CI)
Age at first treatment if at least one risk factor (endometriosis, nulliparity) recorded						
<25 years	<5	#	<5	#	<5	#
25-29 years	44	2.84 (2.06-3.81)***	26	3.28 (2.14-4.80)***	18	2.37 (1.40-3.74)**
30-34 years	97	1.97 (1.60-2.40)***	55	1.86 (1.40-2.43)***	42	2.13 (1.54-2.88)***
35-39 years	93	1.50 (1.21-1.84)***	70	1.67 (1.30-2.11)***	23	1.15 (0.73-1.72)
40-44 years	33	1.11 (0.76-1.56)	24	1.09 (0.70-1.61)	9	1.17 (0.54-2.23)
45+ years	<5	#	<5	#	<5	#
	Trend across categories P<0.001		Trend across categories P<0.001		Trend across categories P=0.01	
Age at first treatment if no risk factors recorded						
<25 years	<5	#	<5	#	<5	#
25-29 years	20	1.42 (0.87-2.19)	<10	#	11	1.57 (0.78-2.80)
30-34 years	45	1.02 (0.75-1.37)	26	1.01 (0.66-1.48)	19	1.05 (0.63-1.63)
35-39 years	41	0.87 (0.62-1.18)	27	0.86 (0.57-1.25)	14	0.89 (0.49-1.50)
40-44 years	17	0.94 (0.55-1.51)	16	1.19 (0.68-1.93)	<5	#
45+ years	<10	#	5	1.21 (0.39-2.82)	<5	#
	Trend across categories P=0.07		Trend across categories P=0.62		Trend across categories P=0.02	

Box S2- Investigation of women with unrecorded cause of infertility

Investigation of women with unrecorded cause of infertility (n= 11,500)

Women with unrecorded cause of infertility had significantly increased rates of breast, ovarian and corpus uteri cancer. Reasons for this are unclear. Those with unrecorded cause of infertility had treatment more recently, at older ages, with fewer cycles, shorter duration of infertility, more 'freeze-all' cycles (data for 'freeze-all' cycles are available for only a sub-set of our cohort; women who had children after assisted conception between 1992 and 2008). Women with unrecorded cause of infertility had a higher cancer incidence within the first 12 months.

Variable	Whole cohort average (95%CI)	Unrecorded cause of infertility cohort average (95%CI)	Test statistic
First treatment year	2002.0 (2002.0-2002.1)	2005.5 (2005.4-2005.5)	P<0.001
Age at first treatment (years)	34.4 (34.4-34.4)	36.3 (36.2-36.4)	P<0.001
Number of treatment cycles	1.77 (1.76 -1.77)	1.51 (1.49-1.53)	P<0.001
Duration of infertility at last treatment cycle	4.90 (4.89-4.92)	3.69 (3.62-3.77)	P<0.001
'Freeze -all' cycle	11.9% (11.7-12.1)	13.2% (12.1-14.8)	-
Proportion of cancers diagnosed within 12months of first treatment.	6.2% (5.3-7.0)	45.7% (37.5-54.0)	P<0.001

Therefore excess risk in this sub-group might be due to reverse causation; cancer and/or related treatment causing infertility rather than arising as a result of infertility or its treatment. Whilst we excluded all women with a cancer diagnosis in calendar years before first treatment year, we could not exclude women diagnosed in the same calendar year as first treatment because exact treatment date was unavailable. As some results remained significant after excluding the first 12 months of follow up, there may be further explanations. Unfortunately study regulations preclude inspection of clinical notes to investigate further.

Table Legends for appendix

Cohort restricted to women who underwent assisted reproduction who were cancer free at least for the first 12 months after the first cycle.

† Absolute Excess Risk per 100,000 person years at risk

‡ 'Breast Cancer'= ICD-9: 1740-9, 2330, 2383; ICD-10: C500-9, D050-9, D486

§ 'Corpus Uteri Cancer'= ICD-9: 1820-8; ICD-10: C54

‖ 'Ovarian Cancer'= ICD-9: 1830-1839, 2362; ICD-10: C56, C570-C574, C481, C482, D391

*P<0.05 **P<0.01 ***P<0.001

¶ See Supplemental Data for results excluding the first 12 months of follow up.

†† 'Invasive Breast Cancer'= ICD-9: 1740-9: ICD-10:C500-9

‡‡ 'In-situ Breast Cancer'= ICD-9: 2330: ICD-10: D050-9

§§ 'Invasive Ovarian Tumours'= ICD-9: 1830-1839 (excluding morphology codes 8442/8451/8462/8472/8473) 2362; ICD-10: C56, C570-C574, C481, C482 (excluding morphology codes 8442/8451/8462/8472/8473).

‖‖ 'Borderline Ovarian Tumours'=ICD-9 1830 (with morphology codes 8442/8451/8462/8472/8473); ICD-10 D391, C56 (with morphology codes 8442/8451/8462/8472/8473).

SIRs suppressed to comply with data disclosure regulations where cells relate to small numbers of individuals. None of the SIRs for affected cells approached significance.

SIR suppressed to comply with data disclosure regulations where cells relate to small numbers of individuals. SIR was significantly lower than age standardised expectation (P=0.014).

REFERENCES

1. Fathalla MF. Incessant ovulation--a factor in ovarian neoplasia? *Lancet* 1971;2(7716):163.

2. Henderson BE, Ross R, Bernstein L. Estrogens as a cause of human cancer: the Richard and Hinda Rosenthal Foundation award lecture. *Cancer Res* 1988;48(2):246-53.

3. Venn A, Watson L, Bruinsma F, et al. Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet* 1999;354(9190):1586-90. doi: 10.1016/S0140-6736(99)05203-4 [published Online First: 1999/11/24]

4. Brinton LA, Trabert B, Shalev V, et al. In vitro fertilization and risk of breast and gynecologic cancers: a retrospective cohort study within the Israeli Maccabi Healthcare Services. *Fertility and sterility* 2013;99(5):1189-96. doi: 10.1016/j.fertnstert.2012.12.029 [published Online First: 2013/02/05]

5. Kallen B, Finnstrom O, Lindam A, et al. Malignancies among women who gave birth after in vitro fertilization. *Hum Reprod* 2011;26(1):253-8. doi: 10.1093/humrep/deq307 [published Online First: 2010/11/20]

6. Yli-Kuha AN, Gissler M, Klemetti R, et al. Cancer morbidity in a cohort of 9175 Finnish women treated for infertility. *Hum Reprod* 2012;27(4):1149-55. doi: 10.1093/humrep/des031 [published Online First: 2012/02/22]

7. Luke B, Brown MB, Spector LG, et al. Cancer in women after assisted reproductive technology. *Fertility and sterility* 2015;104(5):1218-26. doi: 10.1016/j.fertnstert.2015.07.1135 [published Online First: 2015/08/15]

8. Pappo I, Lerner-Geva L, Halevy A, et al. The possible association between IVF and breast cancer incidence. *Ann Surg Oncol* 2008;15(4):1048-55. doi: 10.1245/s10434-007-9800-2

9. Sergentanis TN, Diamantaras AA, Perlepe C, et al. IVF and breast cancer: a systematic review and meta-analysis. *Hum Reprod Update* 2014;20(1):106-23. doi: 10.1093/humupd/dmt034

10. Gennari A, Costa M, Puntoni M, et al. Breast cancer incidence after hormonal treatments for infertility: systematic review and meta-analysis of population-based studies. *Breast Cancer Res Treat* 2015;150(2):405-13. doi: 10.1007/s10549-015-3328-0

11. Rizzuto I, Behrens RF, Smith LA. Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. *Cochrane Database Syst Rev* 2013;8:CD008215. doi: 10.1002/14651858.CD008215.pub2 [published Online First: 2013/08/15]

12. Reigstad MM, Larsen IK, Myklebust TA, et al. Risk of breast cancer following fertility treatment--a registry based cohort study of parous women in Norway. *Int J Cancer* 2015;136(5):1140-8. doi: 10.1002/ijc.29069 [published Online First: 2014/07/22]

13. van Leeuwen FE, Klip H, Mooij TM, et al. Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort. *Hum Reprod* 2011;26(12):3456-65. doi: 10.1093/humrep/der322 [published Online First: 2011/10/28]

14. Stewart LM, Holman CD, Finn JC, et al. In vitro fertilization is associated with an increased risk of borderline ovarian tumours. *Gynecol Oncol* 2013;129(2):372-6. doi: 10.1016/j.ygyno.2013.01.027 [published Online First: 2013/02/07]

15. Stewart LM, Holman CD, Aboagye-Sarfo P, et al. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. *Gynecol Oncol* 2013;128(2):260-4. doi: 10.1016/j.ygyno.2012.10.023 [published Online First: 2012/11/03]

16. Siristatidis C, Sergentanis TN, Kanavidis P, et al. Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer--a systematic review and meta-analysis. *Hum Reprod Update* 2013;19(2):105-23. doi: 10.1093/humupd/dms051 [published Online First: 2012/12/21]

17. Reigstad MM, Storeng R, Myklebust TA, et al. Cancer Risk in Women Treated with Fertility Drugs According to Parity status - A Registry-based Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2017 doi: 10.1158/1055-9965.EPI-16-0809 [published Online First: 2017/01/22]

18. Dor J, Lerner-Geva L, Rabinovici J, et al. Cancer incidence in a cohort of infertile women who underwent in vitro fertilization. *Fertility and sterility* 2002;77(2):324-7. [published Online First: 2002/02/01]

19. Jensen A, Sharif H, Kjaer SK. Use of fertility drugs and risk of uterine cancer: results from a large Danish population-based cohort study. *Am J Epidemiol* 2009;170(11):1408-14. doi: 10.1093/aje/kwp290

20. Rossing MA, Daling JR, Weiss NS, et al. Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994;331(12):771-6. doi: 10.1056/NEJM199409223311204

21. Jensen A, Sharif H, Frederiksen K, et al. Use of fertility drugs and risk of ovarian cancer: Danish Population Based Cohort Study. *BMJ* 2009;338:b249. doi: 10.1136/bmj.b249

22. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The International Glossary on Infertility and Fertility Care, 2017. *Fertility and sterility* 2017;108(3):393-406. doi: 10.1016/j.fertnstert.2017.06.005

23. Scotland ISD. Scottish Cancer Registry: NHS National Services Scotland; 2010 [Available from: http://www.isdscotland.org/Health-Topics/Cancer/Scottish-Cancer-Registry.asp accessed 15th June 2015.

24. Statistics OfN. Cancer Registrations, 1971 to 2011: Office for National Statistics; 2014 [updated 19th June 2014. Available from: http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--43--2012/stb-cancer-registrations-2012.html#tab-Cancer-registrations--1971-to-2011 accessed 15th June 2015.

25. Parkin DM CV, Ferlay J, Galceran J, Storm HH, Whelan SL. Comparability and Quality Control in Cancer Registration. IARC technical Reports. Lyon: International Agency for Research on Cancer, 1994.

26. Breslow NE, Day NE. Statistical Methods in Cancer Research. Lyon, France: International Agency for Research on Cancer., 1987.

27. Stata Statistical Software: Release 12 [program]. College Station Tx: Stata Corp LP, 2013.

28. Adamson GD, Tabangin M, Macaluso M, et al. The Number of Babies Born Globally after Treatment with the Assisted Reproductive Technologies (Art). *Fertility and sterility* 2013;100(3):S42-S42.

29. Stewart LM, Holman CD, Hart R, et al. In vitro fertilization and breast cancer: is there cause for concern? *Fertility and sterility* 2012;98(2):334-40. doi: 10.1016/j.fertnstert.2012.04.019

30. Domar AD, Conboy L, Denardo-Roney J, et al. Lifestyle behaviors in women undergoing in vitro fertilization: a prospective study. *Fertility and sterility* 2012;97(3):697-701 e1. doi: 10.1016/j.fertnstert.2011.12.012 [published Online First: 2012/01/06]

31. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *The Lancet Oncology* 2001;2(3):133-40. doi: 10.1016/S1470-2045(00)00254-0 [published Online First: 2002/03/21]

32. Cetin I, Cozzi V, Antonazzo P. Infertility as a cancer risk factor - a review. *Placenta* 2008;29 Suppl B:169-77. doi: 10.1016/j.placenta.2008.08.007

33. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2014;20(5):748-58. doi: 10.1093/humupd/dmu012

34. Wentzensen N, Poole EM, Trabert B, et al. Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2016;34(24):2888-98. doi: 10.1200/JCO.2016.66.8178 [published Online First: 2016/06/22]

35. Ovarian Cancer Research Fund Alliance (OCRFA). Ovarian Cancer Statistics http://www.ovariancancer.org/about/statistics/2016 [Available from: http://www.ovariancancer.org/about/statistics/ accessed 11th April 2016.

36. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening

(UKCTOCS). *The Lancet Oncology* 2009;10(4):327-40. doi: 10.1016/S1470-2045(09)70026-9 [published Online First: 2009/03/14]

37. Schwarze JE, Valdebenito P, Ortega C, et al. Do women offered assisted reproduction technologies have a higher incidence of gynecologic cancer? A systematic review and meta-analysis. *JBRA Assist Reprod* 2017;21(2):115-19. doi: 10.5935/1518-0557.20170026

38. Jones ME, Swerdlow AJ. Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths. *Am J Epidemiol* 1998;148(10):1012-7. [published Online First: 1998/11/26]