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Breast cancer risk associated with being treated for infertility: results from the French E3N cohort study

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Background: The use of fertility drugs (FDs) is steadily increasing in Western countries and concern has been raised as to the possible impact of fertility treatments on breast cancer risk. **Methods:** We analysed this association in the French E3N study. In this prospective cohort, data on treatment against infertility, duration and time of administration were collected at entry through self-administered questionnaires. Cox regression analysis was used to estimate adjusted relative risks (RRs). **Results:** Among the 92 555 women from the study population, 6602 women were treated for infertility. During the 10 year follow-up period, 2571 cases of primary invasive breast cancer were diagnosed (183 in treated women). Our study showed no overall significant association between breast cancer risk and treatment for infertility (RR = 0.95, confidence interval 0.82–1.11), after surgery or FDs, and whatever the type, the duration of use and the age at first use of FDs. However, infertility treatment was associated with an increased risk, of borderline significance, of breast cancer among women with a family history of breast cancer. This last result had limited statistical power. **Conclusions:** Our study provides evidence that treatment for infertility does not influence breast cancer risk overall. An interaction with a familial history of breast cancer is possible but should be investigated further.

Keywords: *breast cancer/cohort study/fertility drugs/infertility/risk factors*

Introduction

It has been estimated that 14.1% of women in France consult a physician about infertility during their reproductive life (Thonneau *et al*., 1991). Despite a relatively stable prevalence of infertility, defined as the inability to conceive after 1 year of unprotected regular sexual intercourse, the use of fertility services is steadily increasing (Glud *et al*., 1998). In France, this is particularly true in women under 30 years of age.

The two most common causes of female infertility are ovulation deficiency (~32%) and tubal damage (26%) (Thonneau *et al*., 1991). Endometriosis is a third cause, whose prevalence is more difficult to evaluate (between 1 and 50%) according to Schweppe (1988). Ovulation deficiency may have environmental or psychological causes. It can also be due to a number of pathologies characterized by hormonal disorder or by irregular menstruation and ovulation, all of which require treatment. Essentially, treatment is based on a hormonal therapy that stimulates egg development and release by increasing gonadotrophin (FSH and LH) levels at a specific moment in the woman's cycle. The most commonly prescribed drug, clomiphene citrate (CC), competitively blocks estrogen receptors involved in the negative
feedback of estradiol release by the ovaries, which in turn increases the production of FSH and LH.

The pathologies causing infertility and the therapies for these pathologies are associated with major variations in hormonal levels as compared with those of fertile women, and these may be carcinogenic to the breast. Many reproductive factors related to hormone dependence, in particular a high lifetime number of cycles and high levels of endogenous hormones (Kelsey *et al*., 1993; Clavel-Chapelon, 2002) have been shown to be associated with breast cancer risk. Likewise, hormonal treatments such as HRT or oral contraceptives have been associated with a slight increase in breast cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer, 1996, 1997). Epidemiological studies that have explored the risk of breast cancer associated with infertility give rather conflicting results, as reviewed by Klip *et al*.
(2000).

We evaluated the impact of infertility treatment on breast cancer risk, using data from the E3N prospective cohort of ~100 000 women.

Materials and methods

E3N is a prospective cohort study on risk factors for serious diseases, conducted in France. Part of the E3N cohort (i.e. women who replied to a dietary questionnaire) is also included in the European Prospective Investigation into Cancer and Nutrition (EPIC). The cohort consists of 98 997 women, aged 40–65 at entry in 1990, residing in France and insured by the MGEN (Mutuelle Générale de l'Education Nationale), a national health insurance plan primarily covering teachers. Participants were enrolled in the study between June 1990 and November 1991 after replying to a baseline questionnaire. Follow-up questionnaires were sent out at ~24 month intervals.

Women who reported a history of cancer other than basal cell carcinoma at baseline (n = 4567) or for whom no date of diagnosis was available (n = 239) were excluded from the initial pool of 98 997 subjects. Those who reported that they had never had sexual intercourse (n = 1636) were also excluded from analysis. This left 92 555 women for the main analysis.

Information on infertility was recorded in three questionnaires. In the first two, sent out in 1990 and 1992, women were asked whether they had been treated for infertility and, if so, what treatment(s) they had received: fertility drugs (FDs), IVF, surgery or other complementary alternative medicine. The brand names of six drugs were mentioned: Clomid® (CC), Ondogyne® (cyclofenil), Inductor® and Neopergonal® (both HMG), Humegon® (menotrophin, a purified preparation of gonadotrophin) and GCE® (chorionic gonadotrophin). An additional field was provided for other drugs. In 1995, a third questionnaire was sent out to women who had mentioned in any of the first two that they had been treated with FDs. Start and end dates of use were requested for each drug. A total of 4629 answers were obtained, which enabled us to calculate the overall duration of treatment. In cases of inconsistency between the three questionnaires, the dedicated infertility questionnaire (the last one) was chosen as the source.

Information on potential confounders such as reproductive factors (age at menarche, menopausal status, i.e. premenopausal, postmenopausal with natural or with artificial menopause including partial and total oophrectomy, oral contraceptive use, pregnancies and breast feeding), social and anthropometric characteristics [educational level, body mass index (BMI), marital status], personal history of breast disease, family history of breast cancer and smoking habits were recorded at baseline.

All questionnaires asked participants whether cancer had been diagnosed, requesting the addresses of their physicians and permission to contact them. Deaths in the cohort were detected from reports by family members or by the postal service and by searching the insurance company (MGEN) file, which contains information on vital status. Cause of death information was obtained from the National Service on Causes of Deaths (INSERM). Information on the reimbursement of hospital fees of non-respondents to any questionnaires was obtained from the MGEN file. In this case, the subject's physician was contacted for diagnostic information, making it possible to find additional breast cancer cases. Only 1815 women could not be traced in the MGEN file (names misspelt, names changed after divorce, no longer insured with the MGEN, etc.), and nonrespondents in this group were considered lost to follow-up.

For each participant, duration of participation was calculated from the date of return of the first questionnaire up to the date of breast (or other) cancer diagnosis, date of death, date of last questionnaire returned or date of end point (fixed at June 28, 2000).

To investigate the relationship between infertility treatment and breast cancer risk, a proportional hazards regression model (Cox model) was used to estimate the relative risks (RRs) and 95% confidence intervals (CIs) after adjustment for potential confounders. We used age as the time scale to adjust for age properly (Commenges *et al*., 1998), allowing us to express baseline risk as a function of age instead of a function of the time since inclusion. Age is withdrawn from the covariate list. All factors were entered in the model as categorical variables (see Table I for complete coding). Menopausal status was recoded as menopause yes (whatever the reason) or no. Similarly, oral contraceptive was used as a dichotomic variable 'ever consumer' versus 'never'. The variable on a first-degree familial history of cancer gave the number of affected first-degree relatives (mother, sisters or daughters) and that on a personal history of benign breast disease, the number of past

diseases (including mastosis, fibro-cystic disease, cyst and fibro-adenoma). No bivariate analysis was performed due to the large sample size making even slight differences statistically significant. All potential confounding factors were included. Variables not significantly associated with breast cancer risk were subsequently removed. We checked that this did not modify the estimation of other parameters.

Table I: **Description of selected characteristics by infertility treatment and parity. E3N cohort study (n= 92,555 women). 1990-2000.**

	Untreated women (*n*= 85 953)		**Treated women (*n*= 6 602)**	
	Parous (%) (*n*=75 542)	Nulliparous (%) (*n*=10 411)	Parous (%) (*n*=5 216)	Nulliparous (%) (*n*=1 386)
Number of years school				
< 12	13.7	11.0	13.5	12.0
12 - 14	49.7	33.7	42.0	41.1
15 - 16	17.0	18.8	20.0	19.6
≥16	15.4	21.6	21.1	23.8
Missing	4.2	14.9	3.4	3.5
Smoking status at inclusion				
Non smokers	67.0	63.6	62.5	61.6
Former smokers	21.1	21.4	24.6	23.7
Current smokers	11.9	15.0	12.9	14.7
BMI (kg/m²) at inclusion				
<20	17.7	19.5	21.5	19.3
20-25	65.1	64.0	62.4	64.2
>25	17.3	16.5	16.1	16.5
Family history of breast cancer in first-degree				
Ever	11.3	10.8	11.1	10.3
Never	88.7	89.2	88.9	89.7
Personal history of benign breast disease				
Ever	32.0	32.5	36.5	39.4
Never	68.0	67.5	63.5	60.6
Age at menarche (years)				
<12	20.5	19.3	21.2	23.4
12	24.9	23.0	25.3	27.3
13	26.0	33.8	24.2	25.0
14	19.0	15.3	19.3	15.6
≥15	9.6	8.6	10.0	8.7
Menopausal status at inclusion				
Pre-menopausal	52.5	45.7	61.8	51.7
Post-menopausal	37.8	38.4	26.2	39.3
Missing	9.7	15.9	12.0	9.0
Age at first full-term pregnancy (FFTP)				
FFTP before 22	20.2	-	11.3	-
FFTP between 22 and 24	22.9	-	13.4	-
FFTP between 24 and 27	30.7	-	23.6	-
FFTP between 27 and 32	20.1	-	32.6	-
FFTP after 32	6.1	-	19.1	-

Missing data in covariates were treated in two different ways according to the type of covariate. If a value was missing for >5% of all subjects, a separate 'missing' category was created; missing data were otherwise imputed to the modal value.

After exploring the overall relationship between a history of treatment for infertility (pharmacological and non-pharmacological) and breast cancer, we focused on the relationship with FD ever use (including women who declared IVF, since such treatments are generally accompanied by FDs), duration of use and age at first use.

We then explored differential associations between breast cancer and potential confusing factors in women untreated and treated by FDs. We finally investigated the group of women who received any of the thee major fertility drugs: Clomid®, GCE® and Humegon®.

The SAS® v8.2 program was used for all statistical analysis.

Results

Among the 92 555 women (mean follow-up of 9.7 years, SD = 1.4 years), 6602 reported infertility problems. A total of 5216 subsequently gave birth successfully, whereas 1386 (of whom 543 had ever been pregnant) remained nulliparous. Most reported treatments (71.4%) involved FDs. Commonly used drugs were Clomid® (36.2% had ever used this drug), GCE® (28.6%) and Humegon® (12.0%). For the 4629 women who replied to the infertility questionnaire, the mean duration of use was 13 months (±19.6) and the mean age at first use was 30 years (±4.8).

A total of 2571 invasive breast cancer cases with no previous history of cancer were recorded since entry in the study. Of these, 2510 (97.6%) were confirmed by a pathology report. Cases that were only self-reported were also included, as selfreporting proved to be extremely accurate (1.6% false positive).

The distribution of the covariates used as confounders is presented in Table I by history of infertility treatment for parous and nulliparous women. Women treated for infertility problems more frequently had reported a history of benign breast disease than untreated women. They were less corpulent and more often post-menopausal at inclusion. Logically they also had fewer children and their first full-term pregnancy occurred at a later age. Age at menarche and family history of breast cancer were similar across subgroups defined by infertility treatment. We also stratified the population of treated women by parity. The distribution of the main characteristics was comparable between the latter two subgroups, though treated nulliparous women were more frequently premenopausal at inclusion and more often had had a personal history of benign breast disease than treated parous women.

Table II gives the overall association between treatment (both pharmacological and non-pharmacological) and breast cancer. In the whole study population, a history of treatment for infertility was not associated with any change in breast Breast cancer risk associated with being treated for infertility
2217 cancer risk (RR = 0.95, CI 0.82–1.11). A similar result was found with use of fertility drugs (RR = 0.94, CI 0.78–1.12). No modification of the breast cancer risk was found associated with long duration of use of FDs and early age at first use.

Table II: **Adjusted* relative risks (RR) of breast cancer in relation to treatment for infertility. E3N cohort study. 1990-2000.**

	n	PY	Cases	RR[a]	95% CI
Treated for infertility (all treatments)					
Never	85 953	831 342	2 388	1.00[b]	-
Ever	6 602	63 668	183	0.95	0.82-1.11
Treated by fertility drugs (including IVF) only					
Never	85 953	831 342	2 388	1.00[b]	-
Ever	4 834	46 529	133	0.94	0.78-1.12

[a]RR are adjusted for educational level, active smoking, BMI, family history of breast cancer in first-degree relatives, personal history of benign breast disease, age at menarche, menopausal status, composite variable for parity and age at first full-term pregnancy.

[b] Reference category

PY = Person- years

Table III presents interactions between treatment for infertility and some factors reported in the literature as possibly affecting both infertility and breast cancer risk. Risk was similar regardless of BMI, tobacco habits and parity. Women whose menarche occurred after 12 years of age showed an increase in risk, but no pattern of risk across age at menarche strata emerged (results not shown). We found a suggestion of differential risk associated with family history of breast cancer between treated and untreated women. We looked at the subgroup of women who had a first-degree relative with breast cancer (results not presented in the tables). They showed an excess in risk when treated for infertility, as compared with untreated women (RR = 1.37, CI 0.99–1.87), whereas the risk was reduced (RR = 0.86, CI 0.72–1.02) among women with no family history of breast cancer.

Table III: **Adjusted relative risks (RR) in specific sub-groups. E3N cohort study. 1990-2000.**

	Never treated for infertility					Treated by fertility drugs				
	n (85 953)	PY	Cases (2 388)	RR[a]	95% CI	n (4 834)	PY	Cases (133)	RR[a]	95% CI
Number of years school										
< 12	11 528	111 237	273	1.00 [b]	-	433	4 126	9	1.00 [b]	-
12 - 14	41 084	397 689	1 173	1.15	1.01-1.32	2 021	19 472	63	1.49	0.74-3.02
15 - 16	14 761	143 143	387	1.06	0.90-1.25	1 057	10 189	21	1.03	0.47-2.29
≥16	13 893	133 982	435	1.19	1.01-1.39	1 182	11 369	39	1.51	0.72-3.15
Active smoking at inclusion										
Non smokers	57 199	553 548	1 588	1.00 [b]	-	3 000	28 960	82	1.00 [b]	-
Former smokers	18 188	175 961	512	1.02	0.92-1.12	1 202	11 522	39	1.28	0.87-1.89
Current smokers	10 566	101 833	288	1.04	0.91-1.18	632	6 047	12	0.83	0.45-1.52
BMI (kg/m²) at inclusion										
<20	15 365	148 693	431	1.01	0.91-1.13	1 113	10 792	22	0.71	0.45-1.14
20-25	55 827	540 406	1 536	1.00 [b]	-	3 046	29 286	90	1.00 [b]	-
>25	14 761	142 243	421	1.06	0.95-1.19	675	6 451	21	1.03	0.64-1.67
Number of first-degree family history of breast cancer										
0	76 258	738 116	1 965	1.00 [b]	-	4 308	41 523	101	1.00 [b]	-
1	8 877	85 460	374	1.55	1.39-1.74	488	4 646	29	2.32	1.53-3.52
≥2	818	7 766	49	2.14	1.61-2.84	38	360	3	2.77	0.87-8.84
Personal history of benign breast disease										
Never	27 538	264 993	1 133	1.94	1.79-2.10	1 865	17 885	75	2.07	1.46-2.92
Ever	58 415	566 349	1 255	1.00 [b]	-	2 969	28 644	58	1.00 [b]	-
Age at menarche (years)										
≤ 12	38 673	373 720	1 150	1.00 [b]	-	2 273	21 829	59	1.00 [b]	-
> 12	47 280	457 622	1 238	0.86	0.79-0.93	2 561	24 700	74	1.08	0.77-1.53
Menopausal status at inclusion										
Pre-menopausal	44 417	431 130	1 291	1.00 [b]	-	3 067	29 695	84	1.00 [b]	-
Post-menopausal	32 544	312 948	949	0.72	0.64-0.81	1 186	11 209	41	0.81	0.49-1.32
Parity and age at first full-term pregnancy (FFTP)										
Nulliparous	10 411	100 100	320	1.00 [b]	-	1 074	10 310	27	1.00 [b]	-
FFTP before 22	15 258	148 095	346	0.73	0.63-0.86	248	2 405	5	0.90	0.34-2.35
FFTP between 22 and 24	17 311	167 802	440	0.79	0.68-0.92	400	3 848	8	0.91	0.41-2.02
FFTP between 24 and 27	23 209	224 701	629	0.85	0.74-0.97	857	8 325	19	1.00	0.56-1.81
FFTP between 27 and 32	15 181	146 776	486	1.01	0.88-1.16	1 406	13 578	41	1.26	0.77-2.06
FFTP after 32	4 583	43 868	167	1.17	0.97-1.41	849	8 063	33	1.65	0.99-2.75

[a]RRs are adjusted for all covariates presented in the table.

[b]Reference category.

PY = person-years.

None of the drugs investigated here was significantly associated with an excess in risk: RR = 0.96, CI 0.75–1.23, RR = 0.97, CI 0.74–1.27 and RR = 0.99, CI 0.65–1.49 for Clomid®, GCE® and Humegon® use, respectively (see Table IV).

Table IV: **Adjusted relative risks (RR) and 95% confidence intervals (CI) of breast cancer by selected indicators of infertility treatment. E3N cohort study. 1990-2000.**

		n	PY	Cases	RR[a]	95% CI
Specific drugs[b]						
Clomid®	Never received [c]	85 953	831 342	2 388	1.00 [d]	-
	received	2 390	23 089	66	0.96	0.75-1.23
GCE®	Never received [c]	85 953	831 342	2 388	1.00 [d]	-
	Received	1 888	18 203	56	0.97	0.74-1.27
Humegon®	Never received [c]	85 953	831 342	2 388	1.00 [d]	-
	received	789	7 628	23	0.99	0.65-1.49
Overall duration of treatment (months)	Never treated	85 953	831 342	2 388	1.00 [d]	-
	≤ 6	1 549	15 000	45	0.97	0.72-1.31
	> 6	1 516	14 653	43	0.92	0.68-1.24
Age at first use (years)	Never used	85 953	831 342	2 388	1.00 [d]	-
	< 30	1 638	15 862	46	0.98	0.73-1.32
	≥ 30	1 292	12 479	38	0.90	0.65-1.25

[a]Relative risk adjusted for educational level, active smoking, BMI, family history of breast cancer in first-degree relatives, personal history of benign breast disease, age at menarche, menopausal status, composite variable for parity and age at first full-term pregnancy.
[b]Women who had received other treatments exclusively are excluded.
[c]Never received infertility treatment.
[d]Reference category.
PY = person-years

Discussion

Our study showed no significant association between breast cancer risk and treatment for infertility, whatever the type of treatment, the type of drug, the age at first use and the duration of use. Fertility treatments were associated with an increased risk of breast cancer among women with a family history of breast cancer. However, these results had limited statistical power and are probably due to chance, more so as multi-comparisons in subgroups, some of which have <15 000 person-years and <50 cases, inflate the type I error.

Few studies have assessed the risk of breast cancer associated with infertility itself. Klip *et al*. (2000) reviewed 10 cohorts of subfertile women and four case–control studies. Although some subanalyses in these studies concluded that there was a significant association between certain types of subfertility (anovulation, progesterone deficiency, amenorrhoea, tubal or other ovarian disorders) and breast cancer risk (Moseson *et al.*, 1993; Garland *et al.*, 1998), most found no overall relationship (Gammon and Thompson, 1990; Venn *et al.*, 1995, 1999).

However, the lack of power reflected in the very large CIs and the small number of cases limits the statistical inferences of the study of Klip *et al.* (2000). The absence of complete adjustment for known risk factors for both breast cancer and infertility, such as nulliparity or BMI (Grodstein *et al.*, 1994), casts doubts on their conclusions. The use of FDs was not taken into account, except in a subanalysis in Venn's study (Venn *et al.*, 1995). Furthermore, a difficulty underlined by Healy and Venn (2003) which is common to all such studies concerns the reliability of information about the causes of infertility (ovulation disorders or other disorders).

Use of FDs as a risk factor for breast cancer was studied in a few cohort studies. Inconsistent results from six cohort studies with relatively short follow-up times (Ron *et al.*, 1987; Venn *et al.*, 1995, 1999; Rossing *et al.*, 1996; Modan *et al.*, 1998; Potashnik *et al.*, 1999) have shown associations ranging from 0.5 to 2.6. No

clear pattern of risk was apparent (Ricci *et al.*, 1999) whatever the type of treatment and the dose or duration (Burkman *et al.*, 2003). The latest published cohort study (Doyle *et al.*, 2002) did not support any association between ovarian stimulation and increased breast cancer risk (SIR = 116, 84–156). Two case–control studies (Braga *et al.*, 1996; Grabrick *et al.*, 2002) have analysed a possible interaction with family history of breast cancer: they found a non-significant increase, which is compatible with our own result. This increase could suggest that such women are more sensitive to hormonal factors than the general population, as hypothesized by Andrieu *et al.* (1995) to explain the possible interaction between abortions and family history of breast cancer.

Our study offered the opportunity to consider a variety of adjustment factors over a large number of person-years and breast cancer cases. However, in our study, infertility was inferred from the reported use of infertility treatment instead of being based on the usual definition, inability to conceive after 1 year of unprotected regular sexual intercourse. No questions in the E3N questionnaire enquired about delay of conception or desire to conceive. We probably targeted a subset of the whole infertile population, and an unknown proportion of the nulliparous women in our cohort is composed of women who were unaware that they were infertile or who refused to get adequate treatment. Therefore, it was impossible to identify a group of infertile non-treated women that would have served to make an adjustment on infertility. This might also explain the lower prevalence of infertility (percentage of treated women) that we found (7.1%) compared with the figures in the literature (between 8 and 18%; Thonneau *et al.*, 1991). The difference is even greater in the generation born between 1925 and 1934, with a prevalence estimated at 4.4%. The most common FDs came on the market in the late 1960s (Clomid® in 1968 and Humegon® in 1967); on average, such drugs were available during 80% of their reproductive life, as defined by the delay between age 18 and menopause. We therefore also performed subanalyses on women born between 1935 and 1950, for whom such drugs were available during >95% of their reproductive life. We noted no appreciable difference in results for this population.

Another explanation for the lower prevalence in the E3N cohort is the difficulty in accurately remembering drugs taken in past decades. The response rate for the infertility questionnaire was 78%, lower than the usual rate for the follow-up questionnaires but identical to that for the dietary questionnaire, which was similar in terms of complexity. Beyond the fact that infertility has for a long time not been considered a medical issue, the treated women may not all have been fully aware of exactly which treatments were specifically targeting infertility. This underlines both the difficulty of obtaining full information and the importance of prospective studies, which reduce the risk of recall bias. Incomplete data are problematic, especially with regard to duration of treatment. However, a subanalysis of subjects with complete data led to RRs similar to those estimated in the whole population. There was no statistical power for examination of cancer risk by dose of drug, due to limited sample sizes. The majority of studies on cancer risk in fertile women have faced similar limitations.

The population of infertile women who have never received treatment is difficult to identify through self-administered questionnaires. An accurate assessment of infertility requires medical expertise beyond the scope of large cohort studies. We thought it best to define them as women who received treatment for infertility and assumed that our control of confounding factors would counterbalance the presence of false positives to some extent. As >45% of women had reached menopause when they replied to the second questionnaire (90% were >43 years old), we assumed that very few women started fertility treatments afterwards and were not identified for this particular reason. A limitation of the present study is its inability to determine the cause of infertility. Infertility and treatment for infertility may be two independent risk factors of breast cancer, but it is extremely hard to disentangle the effect of infertility on breast cancer risk from that of its treatment. When studying the impact of the treatment, infertility is a perfect example of a confounding factor.

We found no effect of the use of infertility treatment. However, we cannot definitively exclude the possibility that use of fertility treatment increases breast cancer risk in some subgroups and that infertility and its treatment have differential effects on breast cancer susceptibility.

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References

Andrieu N, Duffy SW, Rohan TE, Le MG, Luporsi E, Gerber M, Renaud R, Zaridze DG, Lifanova Y and Day NE (1995) Familial risk, abortion and their interactive effect on the risk of breast cancer—a combined analysis of six case-control studies. Br J Cancer 72,744–751.

Braga C, Negri E, La Vecchia C, Parazzini F, Dal Maso L and Franceschi S (1996) Fertility treatment and risk of breast cancer. Hum Reprod 11, 300–303.

Burkman RT, Tang MT, Malone KE, Marchbanks PA, McDonald JA, Folger SG, Norman SA, Strom BL, Berstrein L, Ursin G, Weiss LK, Daling JR, Simon MS and Spirtas R (2003) Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experience Study. Fertil Steril 79,844–851.

Clavel-Chapelon F (2002) Cumulative number of menstrual cycles and breast cancer risk: results from the E3N cohort study of French women. Cancer Causes Control 13,831–838.

Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 347,1713–1727.

Collaborative Group on Hormonal Factors in Breast Cancer (1997) Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 350,1047–1059.

Commenges D, Letenneur L, Joly P, Alioum A and Dartigues JF (1998) Modelling age-specific risk: application to dementia. Stat Med 17, 1973–1988.

Doyle P, Maconochie N, Beral V, Swerdlow AJ and Tan SL (2002) Cancer incidence following treatment for infertility at a clinic in the UK. Hum Reprod 17,2209–2213.

Gammon MD and Thompson DW (1990) Infertility and breast cancer: a population-based case-control study. Am J Epidemiol 132,708–716.

Garland M, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Spiegelman D, Speizer F and Willett WC (1998) Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. Am J Epidemiol 147,636–643.

Glud E, Kjaer SK, Troisi R and Brinton LA (1998) Fertility drugs and ovarian cancer. Epidemiol Rev 20,237–257.

Grabrick DM, Viernkant RA, Anderson KE, Cerhan JR, Anderson VE and Seller TA (2002) Association of correlates of endogenous hormonal exposure with breast cancer risk in 426 families (United States). Cancer Causes Control 16,333–341.

Grodstein F, Goldman MB and Cramer DW (1994) Body mass index and ovulatory infertility. Epidemiology 5,247–250.

Healy DL and Venn A (2003) Infertility medication and the risk of breast cancer. Fertil Steril 79,852–854.

Kelsey JL, Gammon MD and John EM (1993) Reproductive factors and breast cancer. Epidemiol Rev 15,36–47.

Klip H, Burger CW, Kenemans P and van Leeuwen FE (2000) Cancer risk associated with subfertility and ovulation induction: a review. Cancer Causes Control 11,319–344.

Modan B, Ron E, Lerner-Geva L, Blumstein T, Menczer J, Rabinovici J, Oelsner G, Freedman L, Mashiach S and Lunenfeld B (1998) Cancer incidence in a cohort of infertile women. Am. J Epidemiol 147,1038–1042.

Moseson M, Koenig KL, Shore RE and Pasternack BS (1993) The influence of medical conditions associated with hormones on the risk of breast cancer. Int J Epidemiol 22,1000–1009.

Potashnik G, Lerner-Geva L, Genkin L, Chetrit A, Lunenfeld E and Porath A (1999) Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. Fertil Steril 71,853–859.

Ricci E, Parazzini F, Negri E, Marsico S and La Vecchia C (1999) Fertility drugs and the risk of breast cancer. Hum Reprod 14,1653–1655.

Ron E, Lunenfeld B, Menczer J, Blumstein T, Katz L, Oelsner G and Serr D (1987) Cancer incidence in a cohort of infertile women. Am J Epidemiol 125,780–790.

Rossing MA, Daling JR, Weiss NS, Moore DE and Self SG (1996) Risk of breast cancer in a cohort in infertile women. Gynecol Oncol 60,3–7.

Schweppe KW (1988) In Rock JA and Schweppe KW (eds) Recent Advances in Management of Endometriosis. Parthenon Publishing Group, Lancashire, UK, pp. 13–30.

Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, Lansac J, Lopes P, Tabaste JM and Spira A (1991) Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988–1989). Hum Reprod 6,811–816.

Venn A, Watson L, Lumley J, Giles G, King C and Healy D (1995) Breast and ovarian cancer incidence after infertility and in vitro fertilisation. Lancet 346,995–1000.

Venn A, Watson L, Bruinsma F, Giles G and Healy D (1999) Risk of cancer after use of fertility drugs with in-vitro fertilisation. Lancet 354, 1586–1590.