Subfertility, use of fertility treatments and BRCA mutation status and the risk of ovarian cancer

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Abstract

Purpose The objective of the study is to evaluate the possible association between history of subfertility, fertility treatments, BRCA mutations and the risk of ovarian cancer.

Methods This Israeli National Case–Control study included 1269 consecutive ovarian cancer cases and 2111 individually matched healthy controls. All participants were interviewed and molecular analysis of BRCA mutations were performed to 896 cases. The main outcome measure was reported history of subfertility and exposure to fertility treatments.

Results The rate of reported subfertility was 15.1% and 14.3% in ovarian cancer cases and controls, respectively. However, subfertility was more prevalent in cases with borderline ovarian cancer (but not for invasive ovarian cancer cases) than controls. Multivariate conditional logistic regression revealed that the risk of borderline ovarian cancer was elevated in both women treated for subfertility and those that were not treated for subfertility, (OR = 1.74; 95% CI 0.9–3.36 and OR = 1.79; 95% CI 0.98–3.26, respectively). In non-carriers of BRCA1/2 mutations, fertility treatments were associated with a decreased risk of invasive ovarian cancer while a significant increased risk of borderline ovarian cancer was observed (OR = 2.92, 95%CI 1.67–5.10).

Conclusions Reported subfertility and exposure to fertility treatments were associated with borderline but not with invasive ovarian tumors. This association was more prominent in women who are non-carriers of a BRCA mutation.

Keywords Subfertility · Fertility treatments · Ovarian cancer · BRCA mutations

Introduction

Ovarian cancer represents the sixth most common female cancer in western countries and is the most fatal gynecological malignancy, with 5-year survival rate of approximately 40% [1]. The use of fertility drugs and in vitro fertilization (IVF) is rising worldwide. In Israel, fertility drugs were introduced in 1964 and IVF treatments started in 1982 and are offered free of charge to all women up to the age of 45 for first and second child. For example, the number of IVF cycles that were performed in Israel in 2012 was over 39,000, which is an 80% increase as compared to 2000 [2]. In light of the increasing exposure to fertility treatments (both fertility drugs and IVF), probable sequelae should be investigated.

A number of identifiable factors have been associated with an increased risk of ovarian cancer, including: environmental factors [3], hormonal factors [4], and genetic factors [5]. In particular, the presence of BRCA1 and BRCA2 gene mutations were associated with increased risk for ovarian cancer [6].

A series of articles published by Whittemore et al [7] and Harris et al. [8] in 1992, led to renewed interest in the potential carcinogenic effects of infertility and ovulation inducing drugs. A 2.8 fold increase was observed [7] in the risk for

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invasive ovarian cancer, in women who were exposed to fertility drugs as compared to those who were not. However, case–control studies failed to repeat this finding for invasive ovarian cancer [9–11]. Several cohort studies addressed the same possible association; however, none were able to present an increased risk for invasive ovarian cancer in association with exposure to ovulation inducing drugs [12–20].

The incidence of borderline tumors of the ovary, was found to be elevated in women treated for infertility in several studies published thus far. Shushan et al. [9], in a case–control study, reported an excess risk in the subgroup of women with borderline tumors who had used any fertility drugs (OR = 3.52; 95% CI 1.23–10.09). A Pooled analysis of individual level data from population based case control studies, performed by Ness et al [11], on infertility and fertility drug use, also reported an excess risk of borderline tumors of the ovary in association to infertility and ovulation inducing drug exposure.

Kashyap et al. [21] critically evaluated seven case control and three cohort studies that were published between 1987 and 2000. In this meta-analysis, the results indicated that fertility drugs usage did not increase the risk for ovarian cancer both invasive and borderline. Similar findings were also evident in the recently published meta-analysis by Zhao et al [22].

The notion that BRCA may play a role in the relationship between infertility and Ovarian Cancer has recently been described [23–26]. Considering the frequency of BRCA mutations in Caucasian Ashkenazi population which is over 2% [27] and the high frequency of BRCA mutation in ovarian cancer patients in Israel [28, 29], the implication that BRCA has a possible role in the interaction between infertility and ovarian cancer, warrants further investigation.

The aim of this study was to evaluate the effect of reported history of subfertility and fertility treatments on the development of invasive and borderline ovarian cancer, while adjusting for other established risk factors.

Due to the role of BRCA mutations in ovarian aging and possibly subfertility, BRCA mutation status in association to subfertility among ovarian cancer cases (invasive and borderline), was also analyzed.

Methods

Study population

All Jewish women with pathologically confirmed cancer of the ovary (code 183.0 of the *International Classification of Diseases, 9th Revision, Clinical Modification*), or primary peritoneal carcinoma, possibly of ovarian origin (code 158), diagnosed in Israel between March 1, 1994, and June 30, 1999, were identified. To ensure that no patients with

newly diagnosed cancer were overlooked, all the departments of gynecology in the country, were monitored continually throughout the study, and pathology and oncology departments were checked monthly. During the 5-year study period, 1226 Jewish women were diagnosed with invasive epithelial ovarian cancer (histological subtypes were as follow; serous (n = 567, 44.4%); endometrioid (n = 187, 14.7%), mucinous (n = 65, 5.1%); adenocarcinoma (n = 122, 9.6%); other epithelial (n = 67, 18.4%); clear cell carcinoma (n = 31, 2.4%)). Additional 263 women were diagnosed with borderline histological findings, indicating that the lesion had a low malignant potential. Of these 1489 women, 1269 (85.2%) were interviewed. For each patient, two control women who were matched for age (± 2 years), area of birth, and place and length of residence in Israel (according to defined categories) were selected from the Central Population Registry resulting in 3103 controls; 2111(68%) were contacted and interviewed. All living subjects gave written informed consent. The study protocol, was approved by the Institutional Review Board of Israel and the National Institutes of Health (NIH) review board in the United States of America.

Study instruments

The cases, were interviewed during hospitalization; usually 4 to 6 days after gynecologic surgery and the controls were interviewed at their homes using the same questionnaire. The accuracy and thoroughness of each of the interviewers, were periodically checked, to help ensure that the method of data collections was standardized.

The questionnaire included the following information: demographic and socioeconomic characteristics; smoking habits; family history of cancer; reproductive history including; subfertility; length of use of oral and other contraceptives; age at menarche, age at menopause, length of menstrual cycles, menstrual irregularities, number of pregnancies and births; age at first birth, use of hormone replacement therapy; gynecologic morbidity and procedures. Women were categorized as "infertile", if they answered positively to the question whether they "ever tried to conceive for more than a year". Women classified as "infertile" were further asked whether they received fertility drugs and \ or underwent IVF. In addition, other morbidities; weight at age 18 years, "most of adult life", and "recently" (before illness for cases and 1 year before interview for controls); and height at end of growth, were also reported.

BRCA mutation status

The original study [29] that was conducted between 1994 and 1999, aimed to examine environmental and genetic factors (using family history of cancer) for ovarian cancer. In 1996, when genetic test for BRCA1/2 mutation became available,

a genetic component was added to the study, and blood samples were collected for cases recruited from 1996 onwards. These blood samples were analyzed for the founder mutations as follows:

Biological samples (either peripheral blood or paraffin-embedded tissue sections) were available for cases of ovarian cancer only. These samples were tested for BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) mutations, using genetic laboratory techniques that have been described previously [28]. Briefly, a multiplex polymerase chain reaction, was designed to amplify the exons containing the three mutations with the use of fluorescence-labeled primers in a single reaction. Since each mutation is a small insertion or deletion, it can be detected as a length polymorphism with the use of a genetic analyser (model 310, Applied Biosystems) and Genescan software (Applied Biosystems). These genetic tests, were carried out by the Laboratory of Population Genetics at the National Cancer Institute, Bethesda, MD, USA.

Statistical analysis

Univariable and multivariable conditional logistic regression models, were used to estimate the effect of subfertility with or without fertility treatments, on the risk of ovarian cancer in general and by tumor invasiveness (invasive and borderline tumors). Adjustments for well known risk / protective factors were employed. The controlling variables were: family history of breast / ovarian cancer, oral contraceptive use (women that reported the use of oral contraceptives for a period of less than 6 months were considered as no oral contraceptive use), parity, number of pregnancies, age at first birth, education, BMI and family status. Odds ratios (OR) and 95% confidence intervals (CI) associated with subfertility were estimated. In addition, the association between reported subfertility, fertility treatments and BRCA 1/2 mutations status, were assessed for cases of ovarian cancer only, by tumor invasiveness. In order to evaluate the effect of subfertility and fertility treatments on the risk of ovarian cancer according to BRCA mutation status, a multinomial unconditional logistic regression with all controls as the reference category and adjustment for the above covariates, was applied for the total group as well as by stratification according to tumor invasiveness.

All statistical analyses were performed using the SAS software version 9.1 (SAS institute, Inc, Cary, NC, USA).

Results

No differences were found between the cases and control groups in most of the socio-demographic characteristics (Table 1); 61.2% of the cases had up to 12 years of education, however, significantly more controls than cases had higher education of ≥ 16 years (19.3% vs 15.7%, $p = 0.009$). There were significant differences in family status between cases and controls ($p < 0.001$); more controls than cases were married (71.1% vs. 60.4% respectively), while more cases were single (7.7% versus 3.4% among controls).

Established risk factors for ovarian cancer; family history, obstetric characteristics and obesity were also analyzed. Our results indicate that family history of ovarian and/or breast cancer was significantly more prevalent in cases than controls (12.5% vs. 7.7%; OR = 1.67, 95% CI 1.31–2.12).

Use of Oral contraceptives was more common among controls (19.4% in controls vs. 15.7% in cases, $P = 0.007$). Oral contraceptive use, had a significant protective effect (OR = 0.73, 95% CI 0.58–0.91) for ovarian cancer development.

More cases than controls were never pregnant (10.0% vs. 4.5%). Ever being pregnant, had a protective effect compared with never being pregnant (OR = 0.33, 95% CI 0.24–0.45). Each additional pregnancy significantly reduced the risk for ovarian cancer by 6% (95% CI 0.92–0.97). More cases than controls never gave birth (13.0% vs. 6.6%) and each additional birth significantly reduced the risk for ovarian cancer by 12% (95% CI 0.84–0.92).

The majority of cases and controls were < 30 years old at first birth. Both categories of age (< 30 and ≥ 30 years) at first birth, exhibit a significant protective effect compared to nulliparity (OR = 0.42, 95% CI 0.32–0.54 and OR = 0.37. 95% CI 0.26–0.52, respectively).

BMI of ≥ 30 at most adult life as compared to < 30, was significantly associated with increased risk for ovarian cancer (OR = 1.37, 95% CI 1.10–1.70). Similar associations were also observed, when the cases were stratified by tumor invasiveness to invasive ovarian cancer cases and borderline ovarian cancer cases (supplemental Table 1).

Subfertility was more prevalent in cases than in controls (15.1% versus 14.3%), although not significantly for total ovarian cancer cases. However, this association was significant and more prominent in the borderline ovarian cancer cases (OR = 1.68, 95% CI 1.09–2.60).

Fertility treatments (Table 2) were reported by 7.6% of all cases and 6.3% of the controls; in patients with borderline tumors, the difference was more prominent (13.7% versus 8.0%). In borderline ovarian cancer cases, but not in invasive ovarian cancer cases, an indication for increased risk associated with subfertility treatments was observed (OR = 1.69, 95% CI 0.97–2.95 and OR = 1.03, 95% CI 0.73–1.45, respectively).

There were no women that reported exposure to fertility treatments without reporting subfertility, and 7.5% of the women, reported subfertility without receiving any fertility treatments. In addition, IVF treatments were reported by 33 participants (19 cases and 14 controls). The mean number

Table 1 Distribution of study population by socio-demographic variables and study group

Characteristics	Cases (n = 1269)		Controls (n = 2111)		p
	n	%	n	%	
Age at diagnosis\interview					0.6
Mean ± SD	57.3 ± 13.9		57.1 ± 13.5		
Range	20–87		20–86		
Ethnic origin					
Asia	132	10.4	223	10.6	0.99
North Africa	81	6.4	129	6.1	
Europe–America	741	58.4	1234	58.5	
Israel	315	24.8	525	24.9	
Family status					
Married	766	60.4	1500	71.1	< 0.001
Single	97	7.7	72	3.4	
Divorced/separated/widowed	405	31.9	539	25.5	
Smoking					
Never	868	68.7	1420	67.4	0.4
Past	184	14.6	296	14.0	
Current	212	16.8	392	18.6	
Education (years)					
≤ 8	301	23.9	461	21.9	0.05
9–12	471	37.3	750	35.7	
13–15	292	23.1	487	23.2	
16 +	198	15.7	406	19.3	

Table 2 Reported subfertility and fertility treatments by study group and tumor invasiveness—Univariate analysis

	Total				Invasive				Borderline			
	Cases	Control	OR*	95% CI	Cases	Control	OR*	95% CI	Cases	Control	OR*	95% CI
	n = 1269	n = 2111			n = 1036	n = 1722			n = 233	n = 389		
	%	%			%	%			%	%		
Subfertility												
No subfertility	84.9	85.7	1.0		86.6	85.7	1.0		77.7	85.9	1.0	
Yes, untreated	7.5	8.0	1.0	0.77–1.30	7.2	8.4	0.90	0.67–1.20	8.6	6.2	1.67	0.90–3.10
Yes, treated	7.6	6.3	1.17	0.88–1.56	6.2	5.9	1.03	0.73–1.45	13.7	8.0	1.69	0.97–2.95

*Conditional logistic regression analysis

of IVF cycles was 4.0 with no statistical differences between cases and controls.

Table 3 presents multivariable models for the risk for ovarian cancer, associated with subfertility and adjusted for other known risk factors for ovarian cancer. While the risk associated with subfertility and fertility treatments completely diminished for invasive ovarian cancer cases, the risk associated with borderline ovarian cancer, remained elevated for both treated and untreated infertile women (Adjusted OR = 1.79, 95% CI 0.98–3.26 and Adjusted OR = 1.74, 95% CI 0.90–3.36, respectively). A negative association between education and invasive ovarian cancer, but not borderline

ovarian cancer, was observed. Oral contraceptive use showed a protective effect for both invasive and borderline ovarian cancer development (although only significant in borderline cases). Positive 1st degree family history of breast and\ or ovarian cancer, was found to be a risk factor for both (only significant for invasive ovarian cancer cases).

Molecular analysis for founder mutations in BRCA1/2, was completed successfully in 896 of the 1269 women with epithelial ovarian cancer (779 cases with invasive cancer and 117 with borderline ovarian cancer (Table 4). Of these, 234 women (26.1%) were positive for BRCA mutations (29.4% and 4.3% among women with invasive and borderline

Table 3 Multivariable models for factors associated with ovarian cancer in general and by tumor invasiveness

	Cases (N=1269)	Control (N=2111)	Total (n=1269)		Invasive (n=1036)		Borderline (n=233)	
	%	%	OR	95% CI	OR	95% CI	OR	95% CI
Education								
≤8	23.9	21.9	1.0		1.0			
9–12	37.3	35.7	0.85	0.67–1.08	0.82	0.63–1.06		
13–15	23.1	23.2	0.84	0.64–1.11	0.85	0.63–1.15		
16+	15.7	19.3	0.66	0.49–0.89	0.62	0.45–0.86		
BMI								
<30	82.7	86.8	1.0		1.0			
≥30	17.3	13.2	1.33	1.05–1.67	1.35	1.05–1.74		
Oral contraceptive								
No	84.3	80.6	1.0		1.0		1.0	
Yes	15.7	19.4	0.86	0.68–1.08	0.95	0.73–1.24	0.62	0.39–0.99
Number of pregnancies								
Mean ± SD, continuous	4.0 ± 3.1	4.5 ± 3.1	0.96	0.93–0.99	0.96	0.93–0.99	0.94	0.88–1.01
Family history of breast/ovarian cancer								
No	87.6	92.3	1.0		1.0		1.0	
Yes	12.5	7.7	1.86	1.43–2.43	1.92	1.44–2.55	1.53	0.73–3.21
Subfertility								
No subfertility	84.9	85.7	1.0		1.0		1.0	
Yes, Untreated	7.5	8.0	0.88	0.65–1.19	0.78	0.55–1.09	1.74	0.90–3.36
Yes, Treated	7.6	6.3	0.99	0.72–1.37	0.85	0.58–1.25	1.79	0.98–3.26

Conditional logistic regression analysis also adjusted for family status and age at first birth

ovarian cancer, respectively). 176 women were carriers of BRCA1 mutation and 78 were carriers of BRCA2 mutation.

In women who reported subfertility, 21.0% were positive for BRCA mutations as compared to 27.0% among those who did not report subfertility ($p=0.14$). The risk for subfertility was lower among cases that tested positive for either any BRCA mutation or BRCA1 or BRCA2 controlling for age (OR=0.71, 95% CI 0.46–1.10, $p=0.13$, OR=0.96, 95% CI 0.60–1.51, $p=0.8$ and OR=0.45, 95% CI 0.19–1.06, $p=0.07$; respectively) (not shown). The higher frequency of BRCA mutation carriers in subfertile women, was evident in women who developed invasive ovarian cancer, but not in those who were diagnosed with borderline tumors (27.2% versus 2.9%); 18.6% versus 0 for untreated subfertility in

invasive versus borderline and 38.6% versus 4.8% for treated subfertility. Ovarian cancer cases that reported subfertility without fertility treatments had significantly less BRCA mutations (15.1% versus 27.1%; $p=0.03$). This difference, is mainly attributed to the invasive ovarian cancer group.

Table 5 presents the effect of subfertility and fertility treatments on the risk of ovarian cancer by mutation status. Women carriers of a BRCA1/2 mutation and ovarian cancer patients' non-carriers of BRCA1/2 mutations, were compared with the entire control group. Although fertility treatments were associated with a decreased risk, in women diagnosed with invasive ovarian cancer non-carriers of a BRCA1/2 mutation (OR=0.69, 95% CI 0.43–1.10); a

Table 4 Subfertility and fertility treatments by BRCA gene testing results and tumor invasiveness

		Total			Invasive			Borderline		
		N	% BRCA carriers	p	N	% BRCA carriers	p	N	% BRCA carriers	p
	Total	896	26.1		779	29.4		117	4.3	
	Subfertility			0.08			0.08			0.7
	No subfertility	758	27.0		676	29.7		82	4.9	
	Yes, untreated	73	15.1		59	18.6		14	0	
	Yes, treated	65	27.7		44	38.6		21	4.8	

significant increase in risk was observed among non-carriers with borderline cancer (OR = 2.92, 95% CI 1.67–5.10).

Discussion

Infertility and nulliparity are known risk factors for epithelial ovarian cancer [4]. The present study supports these findings, as cases with ovarian cancer were more likely to have no pregnancies or births, to have their first birth over the age of 30 and to report more infertility than healthy controls. Other known risk factors for ovarian cancer such as family history of breast and/or ovarian cancer were also confirmed in this study. The differentiation between the effect of infertility per se and the possible effect of fertility treatments on ovarian cancer development is not trivial.

The possible link between exposure to fertility treatments and ovarian cancer development has biological credibility and is aligned with the "incessant ovulation" [30] and "gonadotropin" hypotheses [31]. The association between

infertility, fertility treatments and invasive ovarian cancer development, was investigated in numerous case–control [8–11] and cohort studies [12–20, 32–36]. Most case–control studies observed excess risk in infertile women that did not receive hormonal treatments. With the exception of one case–control study [7], all other studies, failed to demonstrate a significant excess risk of invasive ovarian cancer following fertility treatments.

In addition, numerous cohort studies have compared ovarian cancer rates in infertile women with those of the general population. Although cohort sizes were sufficient, most studies failed to present a significant association between exposure to infertility and fertility treatments and invasive ovarian cancer development. Nevertheless, Tworoger et al. [36] observed a significant excess risk for ovarian cancer development in women with female factor infertility. The potential limitations of most of these cohort studies are the small number of ovarian cancer cases, as well as lack of information regarding significant confounding factors. Some of the cohort studies [21] included an internal comparison

Table 5 Effect of subfertility and fertility treatments on the risk of ovarian cancer by mutation status and tumor invasiveness

Total epithelial

	Carriers (BRCA +) cases N = 234				Non carriers (BRCA –) cases N = 662				Control N = 2111	
	n	%	OR*	95% CI	n	%	OR*	95% CI	n	%
Subfertility										
No subfertility	205	87.6	1.0		553	83.5	1.0		1810	85.7
Yes, untreated	11	4.7	0.61	0.31–1.19	62	9.4	1.06	0.75–1.48	168	8.0
Yes, treated	18	7.7	1.14	0.65–2.01	47	7.1	1.07	0.73–1.56	133	6.3

Invasive

	Carriers (BRCA +) cases N = 229				Non carriers (BRCA –) N = 550				Control N = 1,722	
	n	%	OR*	95% CI	n	%	OR*	95% CI	n	%
Subfertility										
No subfertility	201	87.8	1.0		475	86.4	1.0		1476	85.7
Yes, untreated	11	4.8	0.63	0.30–1.16	48	8.7	0.92	0.62–1.33	144	8.4
Yes, treated	17	7.5	1.08	0.61–1.93	27	4.9	0.69	0.43–1.10	102	6.3

Borderline

	Carriers (BRCA +) cases N = 5				Non carriers (BRCA –) N = 112				Control N = 389	
	n	%	OR**	95% CI	n	%	OR**	95% CI	n	%
Subfertility										
No subfertility	4	80.0	1.0		78	69.6	1.0		334	85.9
Yes, untreated	0		–		14	12.5	1.68	0.89–3.12	24	6.2
Yes, treated	1	20.0	1.29	0.13–12.5	21	18.8	2.92	1.67–5.10	31	8.0

*The estimates are adjusted for education, BMI, family status, age at 1st birth and 1st degree family history of breast/ovarian cancer

**Adjusted for education, BMI, age at 1st birth and 1st degree family history of breast/ovarian cancer

between infertile women who were treated with fertility treatments and those who were not, with similar results. Recent publications failed to observe an increased risk for invasive ovarian cancer [21, 32, 33].

In the present study, approximately 30% of women with invasive ovarian cancer were found to be BRCA positive. However, infertile women as compared to fertile, were less likely to be BRCA positive (although not significantly). In a cohort study that followed over 2500 Israeli infertile women, 12 women developed invasive ovarian cancer, none of which was positive for BRCA mutations [26]. Recently, Perri et al [23] investigated whether BRCA mutation carriers who undergo fertility treatment are at increased risk of developing invasive ovarian cancer and found that fertility treatments were not associated with invasive ovarian cancer risk. Similar findings were also observed by Grownwald et al [25]. In light of information regarding the possible association of BRCA1 mutations with occult primary ovarian insufficiency [24]. a recent review [37], assessed the role of BRCA mutations and ovarian aging. BRCA and especially BRCA1 function in DNA repair is decreasing with age in the human oocytes. Therefore, women with BRCA 1 mutations might have lower ovarian reserves and experience earlier menopause, leading to infertility. Moreover, Ponce at al [38] measured the levels of anti-Mullerian hormone (as a proxy for infertility) in BRCA carriers. Women that were positive for BRCA 2 had lower levels of anti-Mullerian hormone and higher probability of infertility (although not statistically significant) as compared to BRCA1 carriers and BRCA mutation-negative women.

Due to the controversy regarding the role of BRCA mutation and ovarian function, larger studies regarding the association between types of infertility, BRCA and subsequent development of ovarian cancer, should be conducted.

In our study, while the association between subfertility and invasive ovarian cancer was not observed, cases with borderline tumors reported significantly more subfertility (adjusted OR = 1.76, 95% CI 1.10–2.82). The risk for borderline tumors of the ovary in infertile women was found to be significantly increased in both case control [8, 9, 11] and cohort studies [13, 33–35, 39], with magnitude ranging from 1.76 to 4.00, for various fertility treatments.

Borderline tumors of the ovary present a unique entity of ovarian malignancy with less family history, less detection of BRCA mutations, higher incidence of estrogen receptors, younger age at diagnosis and significantly higher 5 years survival rates [40–42], as compared to invasive ovarian cancer. Therefore, the different role of subfertility in borderline tumors may also support the distinct etiology of these tumors. Since borderline tumors of the ovary may be diagnosed due to surveillance, especially in women exposed to fertility treatments (which requires repeated ultrasonographic examinations), the association between subfertility and borderline tumors may represent surveillance bias.

Being a BRCA carrier was not significantly associated with borderline tumor development and women with borderline tumors had much lower rates of BRCA positive tests (4.3%). However, women with subfertility that were treated, were tested positive for BRCA, at higher rate than women with no reported subfertility, although this finding was not significant.

One of the strengths of our study is that in Israel, infertility treatments, are covered by the national health insurance law, for first and second child to every woman under the age of 45 years. As a result, our study population was non-selective. Nevertheless, Israel's relatively small population, limited the number ovarian cancer cases and especially borderline tumors that could be investigated. Due to the case–control design of the present study, information regarding subfertility and fertility treatments (including type and dose) was obtained, only by self-reporting from the women and therefore, may be incomplete and/or subjected to recall bias. However, women reported both subfertility problems and use of fertility treatments, therefore representing better validity of the information. Unfortunately, specific data regarding doses of IVF treatments was not available. In addition, the present study that investigated a representative unselected population, attempted to evaluate the role of BRCA mutation status, in association to subfertility and fertility treatments and ovarian cancer, a topic that only very limited number of studies addressed. Moreover, the present study investigated subfertility in women that were already diagnosed with either invasive ovarian cancer or borderline ovarian tumors, with association to their BRCA mutation status, while other publications reported the association of subfertility and BRCA mutation, regardless of ovarian cancer morbidity.

Conclusions

Results regarding the possible association of subfertility, fertility treatments and invasive ovarian cancer, as observed in the present study, show no increased risk and therefore, support previous reassuring publications.

Different risk factors, were found to be associated with invasive ovarian cancer and borderline tumors. In light of the possible association between subfertility and borderline ovarian tumors, but not invasive ovarian cancers, which has also been reported by others, further consideration needs to be given to the distinction between these two types of tumors in terms of hormonal exposures, both intrinsic (types of infertility) and extrinsic (types and dose of fertility

treatments). Further studies targeted to borderline tumors of the ovary, are needed to support this finding.

Appendix

Nationall Israeli Study of Ovarian Cancer

The members of the National Israeli Study of Ovarian Cancer are:Shmuel Anderman, MD; Marco Altaras, MD; Shaul Anteby, MD; Jack Atad, MD; Amiram Avni, MD; Amiran Bar-Am, MD; Dan Beck, MD; Uzi Beller, MD; Gilad Ben-Baruch, MD; Yehuda Ben-David, MD; Haim Biran, MD; Moshe Ben Ami, MD; Angela Chetrit, MSc; Shulamit Cohan, MD; Ram Dgani MD; Yehudit Fishler, CTR; Ami Fishman, MD; Eitan Friedman, MD; Ofer Gemer, MD; Ruth Gershoni, MD; Walter Gottlieb, MD; Reuvit Halperin, MD; Galit Hirsh-Yechezkel, PhD; David Idelman, MD; Rafael Katan, MD; Yuri Kopilovic, MD; Efrat Lahad, MD; Liat Lerner Geva, MD; Hanoch Levavi, MD; Albert Levit, MD; Tally Levy, MD; Beatriz Lifschiz-Mercer, MD; Flora Lubin, MSc, RD; Zohar Liviatan, MD; Jacob Markovich, MD (deceased); Joseph Menzcer, MD; Baruch Modan, MD (Chairman, deceased); Hedva Nitzan, RN, MPH; Moshe Oettinger, MD; Tamar Peretz, MD; Benjamin Piura, MD; Shulamit Rizel, MD; Siegal Sadetzki, MD; Adi Shani, MD; David Schneider, MD; Michael Shtark, MD; Mariana Shteiner, MD; Zion Tal, MD; Chaim Yaffe, MD; Ilana Yanai, MD; Shifra Zohar, MD; and Ahuva Zoltan, RN, BA.

Declarations

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