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The goal of this project is to determine whether oral contraceptives (OCs) and parity are as protective against ovarian cancer in BRCA ½ carriers as they are for women in general (Specific Aim 1). The second goal is to determine whether there are survival differences between BRCA 1/2 carriers with ovarian cancer compared to women with sporadic disease (Specific Aim 2). The study employs a case-case design. We identified Jewish women with epithelial ovarian cancer. We genotyped these women for the 3 BRCA1/2 mutations found in Ashkenazi women. We compared oral contraceptive use and parity between carriers and non-carriers. We will also compare survival differences between the two groups.

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INTRODUCTION:

The goal of this project is to determine whether oral contraceptives (OCs) and parity are as protective against ovarian cancer in BRCA1/2 carriers as they are for women in general (Specific Aim 1). The second goal is to determine whether there are survival differences between BRCA1/2 carriers with ovarian cancer compared to women with sporadic disease (Specific Aim 2). The study employs a case-case design. We identifed Jewish women with epithelial ovarian cancer. We genotyped these women for the 3 BRCA1/2 mutations found in Ashkenazi women. We compared oral contraceptive use and parity between carriers and non-carriers. We will also compare survival differences between the two groups.

BODY:

This research had two specific aims. Specific aim 1 was accomplished and resulted in one conference presentation (1) and one publication (2) (see appendix 1).

Specific aim 2 has not been accomplished. The recent changes in regulations due to HIPAA has resulted in our not being able to obtain the data and specimens as initially outlined. We have therefore requested a 1 year no-cost extension to continue to pursue this aim.

We have original IRB approval from 3 hospitals, which house a total of over 400 eligible cases for specific aim 2: North Shore University Hospital (289 specimens – Andrew Menzin, MD, co-investigator), Long Island Jewish Hospital(88 specimens, A. Menzin, co-investigator) and Northwestern University Hospital (101 specimens, David Fishman, MD, co-investigator).

We have obtained 45 specimens from N. Shore University Hospital. An additional 51 specimens are waiting for release from Northwestern University Hospital Specimen retrieval includes a block of tumor tissue, a block of normal tissue, a slide of the tumor and a slide of the normal tissue. A pathology report accompanies all specimens. Once the specimens and accompanying path report is received, Dr. Naus (the study pathologist in Pittsburgh) reviews the slides and report to confirm eligibility of the specimens for the study. Eligibility criteria include: diagnosis of invasive epithelial ovarian cancer between Jan 1, 1990 and Dec 31 2001. To date, all specimens have met our criteria.

Dr. Naus also confirms the histological subtype of the tumor as well as tumor grade using the slides and data sent from the sites. Thus far, we have had no discrepancies between the original pathology report and Dr. Naus' review.

We are requesting both tumor and normal tissue for two reasons. First, we will do our genotyping on the normal tissue to ensure we truly identify a germline mutation in the BRCA/2 genes. Second, we are banking the tumor and normal tissue in anticipation of future research. For example, we intend to look at mechanisms of BRCA inactivation (such as LOH and methylation) as they affect response to chemotherapy and survival. Thus, our efforts in this project are also supporting future research.

Because access to medical records is now limited, we have made arrangements with all sites to obtain the relevant data in a blinded fashion from the tumor registrar. Attached is the set of variables being requested on each subject. These variables were developed in conjunction with an ovarian cancer tumor registrar to ensure

that they are universally available from all tumor registries in the study. Appendix 2 contains the list of variables.

Laboratory Assays:
We tested our laboratory assays on a sample of 36 specimens The laboratory assays are performed in the laboratory of Dr. Jeffrey Kant in the Division of Molecular Diagnostics at the University of Pittsburgh Medical Center. The Division currently performs clinical BRCA1/2 screening for the Ashkenazic Jewish mutation panel using allele-specific hybridization (ASO) and direct DNA sequencing approaches. These assays employ polymerase chain reaction (PCR) amplification in which several gene regions are co-amplified, spotted and hybridized to wild type and mutant probes, and detected by chemiluminescence. Samples testing positive for a mutation are confirmed by DNA sequence analysis using an ABI Model 373 semi-automated DNA sequencer.

For quality control purposes, a subset of 8 specimens were sent to the laboratory in a blinded duplicate fashion. The findings for the 8 specimens were concordant, providing confidence in the laboratory quality. For quality control purposes, we have decided to batch the genotyping of the remaining specimens during year 3 of the study. Thus, we have not done any additional genotyping.

DNA for this study is obtained from paraffin sections. Two 5-10 micron tissue sections are processed. Excess paraffin is removed by razor blade. The sections are dewaxed in xylene, washed in ethanol, and suspended in a Tris-EDTA-Triton X-100 extraction buffer. An overnight proteinase K digestion is then performed at 56 degrees Centigrade. The proteinase K is heat-killed by boiling. Finally, the solution is pelleted at high speed, and the extract saved for subsequent analysis. A commercial kit method (Puregene by Gentra) has also worked successfully in our hands. To ensure that we identify germline mutations (not somatic) wherever possible we isolate DNA from the normal tissue block. Thirty two of the 34 specimens from NY contained both a tumor and normal block; only 2 contained only a tumor block. Dr. Stanek informed us that he was unable to identify a normal block on those two women.

Exons 2 and 20 of BRCA1 as well as the portion of BRCA2 exon 11 containing nucleotide 6174 are amplified by a 35-cycle multiplex polymerase chain reaction. Amplicons are then denatured, filtered onto positively-charged nylon support substrates, and hybridized to separate oligonucleotide probes (5'-conjugated with alkaline phosphatase) that detect wild type and mutant sequences. Heterozygous controls are included for reactions as well as minus-DNA blanks. Following hybridization and washing, blots are developed with the chemiluminescent substrate, Lumi-Phos. Results are scored by visual inspection of autoradiograms after brief exposure.

Problems encountered and measures taken:

The major problems we have encountered include

1). Obtaining HIPPA compliant IRB approval for this study at participating sites
2). Obtaining specimens from the approved sites

To address problem #1, we have redesigned the study so that all data and information is extracted by a third party and we receive the data in a blinded fashion. In addition, instead of doing chart reviews, we will obtaian the relevant data from the tumor registrars at each site. We will have no way to identify the subjects in the study.

To address problem 2, we are working more closely with the investigators at the three sites. We acknowledge that the New York hospital sites have been delayed in sending us specimens. This was due to a change in

research team members at that site. That change resulted in the project being put on hold for almost a year. A new pathologist at that site has been obtained (Dr. Stanek), and we have begun once again to work with the investigators to move the project forward. We feel confident in Drs. Menzin and Stanek's commitment to the project and anticipate its successful completion.

We have been working with Dr. David Fishman at Northwestern University. Since the IRB was approved in May, we have identified the 101 eligible specimens and are working with his group to perform the necessary chart reviews and obtain the pathology specimens.

Personnel Supported

Jeff Kant, MD - laboratory assays
Greg Naus, MD – pathologist
Pam Overberger – research assistant
Glenn Allen – research assistant
Randi Koenig - research assistant

KEY RESEARCH ACCOMPLISHMENTS:

We identified a series of 242 Ashkenazi Jewish women with invasive epithelial ovarian cancer. These women had participated in two population-based case control studies, a genetic counseling center at Northwestern University and a multi-center study of Jewish women with ovarian cancer. Thirty-six of the 242 women were the cases we identified in year one of the current study. We obtained BRCA1/2 genotyping data and reproductive data on these 242 women. We analyzed these data to determine the association between OC use and ovarian cancer risk in *BRCA1/2* carriers. Oral contraceptive use, childbearing and breastfeeding appear to protect *BRCA1* and *BRCA2* carriers from ovarian cancer, as they do for women in the general population. A manuscript detailing these findings was published in 2003 and is attached (ref 2).

REPORTABLE OUTCOMES:

Two publications and one presentation resulted from this work. An abstract and presentation were given at the American Society for Human Genetics 2001 (ref 1).

A manuscript detailing the research was published in Cancer Causes and Control 2003 (ref 2)

Based on this work, Dr. Modugno applied for and received funding from the NCI to pursue additional endpoints examining risk modifiers of ovarian cancer in BRCA1/2 carriers (R03CA92776).

CONCLUSIONS:

In conclusion, our initial findings suggest that both OC use and childbearing are protective in *BRCA1/2* carriers and non-carriers. We are currently working towards the survival and treatment endpoint in our population.

We are concerned that due to delays at our sites, we will be delayed in completing Specific Aim 2. While we are confident that we will complete the work tasks as outlined in the original proposal, we are concerned that we will not meet these goals on time. We have requested and been granted a one year no-cost extension from the DOD so that we complete the work as outlined in our proposal. We are working closely with Dr. Bora, project officer at the DOD, to ensure the completion of this study.

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2. Francesmary **Modugno,** Roxanna Moslehi, Roberta B Ness, Deborah Brookes Nelson, Steven Belle, Jeffrey Kant, James Wheeler, Aimee Wonderlick, David Fishman, Beth Karlan, Harvey Risch, Daniel Cramer, Marie-Pierre Dube, Steven Narod. Reproductive Factors and Ovarian Cancer Risk in Jewish BRCA1 and BRCA2 Mutation Carriers. *Cancer Causes and Control* 2003; 14(5):439-446.

APPENDICES:

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Tumar Registry data variables.

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Reproductive factors and ovarian cancer risk in Jewish *BRCA1* and *BRCA2* mutation carriers (United States)

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Key words: *BRCA1*, oral contraceptives, ovarian cancer, parity.

Abstract

Objective: To determine whether oral contraceptive (OC) use, childbearing, breastfeeding and tubal ligation differ between ovarian cancer cases with and without a *BRCA1/2* mutation.

Methods: A case-only study of 242 Jewish women with invasive epithelial ovarian cancer. Women were genotyped for three Ashkenazi founder mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*). We obtained data on OC use, childbearing, breastfeeding, gynecologic surgeries and other reproductive factors from each woman. We compared the frequencies of these risk factors in carriers and non-carriers using unconditional logistic-regression, controlling for other covariates.

Results: Among the 242 cases, 64 (26.4%) carried one of the *BRCA1* founder mutations, and 31 (12.8%) carried the *BRCA2* mutation. Although there were no differences in the percent of nulliparous women between carriers and non-carriers, parous *BRCA1* carriers reported fewer live births than non-carriers (average of 2.1 *versus* 2.5 live births, OR = 0.61, 95%CI = 0.39–0.95, adjusted for age at diagnosis, tubal ligation and duration of OC use). Carriers and non-carriers did not differ in their history of breastfeeding, or in their lifetime use of OCs. *BRCA1* carriers were more likely than non-carriers to have had a tubal ligation (25.0 *versus* 10.2%, OR = 3.67, 95%CI = 1.55–8.70, adjusted for age at diagnosis, number of live births and OC duration).

Conclusions: In general, OC use, childbearing and breastfeeding do not differ between *BRCA1/2* carriers and non-carriers with ovarian cancer. However, the effects of tubal ligation may differ between *BRCA1* carriers and non-carriers.

Introduction

Mortality from invasive ovarian cancer is very high, with a five year survival rate of approximately 40% [1]. Survival is better with early stage disease, but the majority of patients present with metastatic disease [1]. To date, no effective early detection techniques have been identified and primary prevention represents an important opportunity for reducing ovarian cancer morbidity and mortality. Women with mutations in the cancer predisposing *BRCA1* and *BRCA2* genes have a lifetime ovarian cancer risk of 16–36% [2–5]. Using oral contraceptives (OCs), bearing children and

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breast-feeding have consistently been shown to reduce ovarian cancer risk among women in general [6, 7]. Tubal ligation has also been shown to reduce ovarian cancer risk [6, 8]. However, little is known about the impact of these factors on ovarian cancer risk in *BRCA1/2* mutation carriers. In a case–control study comparing 207 women with hereditary ovarian cancer to 161 of their unaffected sisters without the disease, OC use was less common among women with the disease [9]. This suggests that OC use may reduce the risk of ovarian cancer in women with a mutation in the *BRCA1* or *BRCA2* genes. However, the results of that study have been questioned, because the *BRCA1/2* carrier status of some of the sisters was unknown. This unknown data can potentially invalidate the findings. More recently, a case–control study of Israeli Jewish women found that the risk of ovarian cancer among carriers of a *BRCA1* or *BRCA2* mutation decreases with each birth but not with increased duration of use of oral contraceptives [10]. These conflicting data suggest the need to further investigate the potential of OCs as a chemopreventive agent among women with a *BRCA1/2* mutation.

In this study, we aimed to evaluate the potential benefit associated with OC use among women at high risk for ovarian cancer because they carry a mutated *BRCA1* or *BRCA2* gene. We also sought to determine the benefit or risk associated with other reproductive factors, including childbearing, breastfeeding, and tubal ligation in these women.

Methods

Subjects

Because of the high prevalence of three *BRCA1/2* founder mutations among Ashkenazi Jewish women with invasive epithelial ovarian cancer [11], we limited our study to Jewish women with epithelial ovarian cancer and with no prior history of breast cancer. Data on subjects were pooled from four sources: two population-based case–control studies of epithelial ovarian cancer in the United States (100 cases) [12, 13], a hospital-based study of Jewish women with epithelial ovarian cancer among 11 centers in North America and Israel (208 cases) [11], and a genetic counseling center in Chicago (14 cases). The Chicago clinic had been one of the sites for the hospital-based study, but the 14 incident, invasive cases included in this analysis were in addition to those participating in the original study. There was some overlap between cases included in the current study and those in the previous report of OCs and ovarian cancer in *BRCA1/2* carriers [9] but this was less than 10%. Unfortunately, because subject links from the original studies to this study were not maintained, we were unable to identify which cases included in this study were also included in the previous report of OCs and ovarian cancer [9].

Moslehi *et al.* [11] (the hospital-based study) classified a woman as Jewish if three out of four grandparents were Jewish. Questions about place of birth of parents and grandparents further identified Ashkenazi women in that study. In Lu *et al.* [13] (one of the population-based studies), a woman was considered to be Jewish if she indicated that her childhood religious upbringing was Jewish. For the other two sources of subjects, a woman was considered to be Jewish if she classified herself as Jewish on medical records.

Specific descriptions of each study methodology are provided in the original publications [11–13] and are summarized in Table 1. Briefly, Moslehi *et al.* [11] used medical records to identify 465 Jewish women with ovarian cancer. Of these, 80 women were dead, 33 women were found not to have invasive disease on pathology review, 98 women were unreachable, and 49 women refused to participate. The remaining 208 (44.7%) women completed an in-person interview and provided a blood sample. Ness *et al.* [12] identified all women age 20–69 diagnosed with ovarian cancer in the Delaware Valley between 1994 and 1998. Of the 957 eligible women, 69 were too ill to participate, 15 were untraceable, and 92 refused to participate. Fourteen physicians did not consent to their patients' participating, for a total of 767 (80.1%) eligible women who completed an in-person interview. For the study presented here, we used medical records to identify successfully the religious affiliation of 437 of the 767 women, 46 of whom were Jewish, and we used banked pathology specimens (normal tissue blocks) to determine *BRCA1/2* carrier status of 36 of these women. Lu *et al.* [13] used tumor registries to identify 1080 women with ovarian cancer in eastern Massachusetts and New Hampshire between May 1992 and March 1997. Of the 1080 women, 203 had died or were unreachable, 126 were not contacted because their physician denied permission, 136 women declined participation, and 52 had non-epithelial ovarian cancer. The remaining 563 (52%) women were interviewed, during which time they provided a blood sample and answered questions about their childhood religious upbringing. Of the 563 women, 54 identified Jewish as the religion of their upbringing.

Each study obtained written informed consent from participants and was approved by the appropriate institutional review boards.

Table 1. Summary recruitment and eligibility characteristics of four pooled studies

Study	Moslehi *et al.* [11]	Ness *et al.* [12]	Luc *et al.* [13]	Chicago	Present study
Year of diagnosis	1980–1999[a]	1993–1998	1992–1997	1990–1999	1990–1999
Place	11 centers in North America and Israel	Delaware Valley, USA	Massachusetts and New Hampshire	Chicago	na
Total eligible	465	957	1080	14	na
Total participants	208	767 (437 with known religion)	563	14	na
Method of determining Jewish descent	3 of 4 grandparents Jewish	Self disclosure of current religion	Childhood upbringing	Self disclosure of current religion	na
Total eligible Jewish women	208	46	54	14	322
Total with complete exposure data	191	46	54	14	305
Total with *BRCA1/2* status known	191	36[b]	54	14	295
Total confirmed invasive	162	31	35	14	242
Total with *BRCA1/2* founder mutation	65	15	13	2	95

[a] 26/162 final participants included in this analysis were from 1980–1989; 1 final participant was from 1972.
[b] Ten tissue blocks were unobtained.

Exposure information, BRCA1/2 mutation status and data quality

From each study source, data were requested on the use of OCs, including age at first and last use, and duration of use. Data were also obtained on number of live births, age at first and last live birth, and total duration of breastfeeding. We further requested information on other factors including age at menarche, body mass index, history of hysterectomy and history of tubal ligation. Because data on age at menopause and hormone replacement therapy were inconsistent among the studies, we were not able to include them in our analyses. We obtained details of tumor histology on all subjects, and we restricted our analyses to invasive ovarian cancers of the epithelial type. All data were checked for internal consistency and corrections or clarifications were requested from the original investigators when necessary.

All subjects were screened for the three Ashkenazi founder mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*) Mutation analysis was performed by the original study investigators using several established detection techniques, including heteroduplex analysis, single-strand conformation analysis and allele-specific oligonucleotide hybridization. In addition, Moslehi *et al.* [11] tested all subjects for mutations in exon 11 of *BRCA1* and exons 10 and 11 of *BRCA2* using the protein-truncation test [14]. Truncating mutations in these exons represent about 70% of the *BRCA1/2* mutations found to date [11]. No women from that study included in the analysis reported here were found to have any *BRCA1/2* mutations other than one of the three *BRCA1/2* founder mutations. Regardless of the technique employed, all mutations were confirmed by direct sequencing of DNA. Non-carriers were defined as women with none of the three mutations (for the studies employing only the Ashkenazi panel) and no other detected mutations (for subjects from Moslehi *et al.* [11]). *BRCA1* carriers were defined as women with either the 185delAG or the 5382insC in *BRCA1*. Women with the 6174delT in *BRCA2* were defined as *BRCA2* mutation carriers.

All subject data submitted for the pooled analysis were anonymous. Approval for the pooled analysis was obtained from the University of Pittsburgh Institutional Review Board.

Study design and statistical analyses

To determine whether carriers and non-carriers differed in OC use, parity, breast-feeding, and tubal ligation, we employed a case-only study design [15]. In a case-only study, cases with the genotype (carriers) form the 'pseudo-cases' and cases without the susceptibility genotype (non-carriers) form the 'pseudo-control' group. The two groups are compared with respect to the prevalence of each exposure. The odds ratio (OR) reflects the association between the exposure and the genotype (assuming independence of genotype and exposure). If this ratio is different from one, then the relative risk associated with the exposure differs for carriers and non-carriers. For a protective factor such as OC use, childbearing and breastfeeding in ovarian cancer, an OR greater than one indicates that the factor was more prevalent among the carriers ('pseudo-cases');

thus, the factor provides less protection to carriers than to non-carriers. Conversely, an OR of less than one indicates that the factor was less prevalent among the carriers, and suggests that the factor provides greater protection for carriers than for non-carriers.

To control for potentially confounding effects of other factors, we used unconditional logistic-regression analyses and included as covariates age at diagnosis and year of birth as continuous terms. Age at diagnosis was included in all models because univariate analyses showed a significant difference between carriers and non-carriers. Because the studies differed in the time period in which they were performed, year of birth was included in order to control for secular trends in OC use, parity and breastfeeding. However, there were no differences in results between analyses including year of birth and those excluding the variable. We therefore present the most parsimonious model in this paper. To check the reasonableness of pooling data from diverse sources, we calculated a Mantel–Haenszel test for heterogeneity for all major results. In none of the associations between BRCA status and reproductive factors did we find statistically significant heterogeneity among subject source. In addition, models that included a variable for study site did not differ in results from models excluding the variable; thus, the final models presented in this paper do not include a variable for study site. All analyses were performed with the STATA statistical software package (STATA Corporation, Release 5.0) and all p values given are from two-sided tests.

We analyzed all cases with complete exposure data. Because one of the parent studies [11] noted a difference in age at onset between *BRCA1* and *BRCA2* carriers, and because univariate analyses showed other differences in risk factors between *BRCA1* and *BRCA2* carriers for the entire study population, we analyzed the data for *BRCA1* and *BRCA2* carriers both jointly and separately.

Results

Table 1 presents a summary of the subjects participating in this study from the four parent studies. A total of 322 cases of epithelial ovarian cancer in Jewish women were identified. Of these, complete exposure data were obtained on 305 cases and *BRCA1/2* status was confirmed on 295 cases. Of the 295 cases, invasive histology was confirmed on all but 53 cases, for a total of 242 cases included in this analysis.

The characteristics of the 64 subjects with a *BRCA1* mutation, the 31 subjects with a *BRCA2* mutation, and the 147 non-carriers are presented in Table 2. As expected, *BRCA1* carriers with invasive tumors were diagnosed at a significantly earlier average age than non-carriers (51.2 *versus* 57.5 years, $p = 0.001$). In contrast, *BRCA2* carriers were diagnosed at later ages than non-carriers (60.8 *versus* 57.5 years), although this difference was not significant. The difference in age at diagnosis between *BRCA1* carriers and *BRCA2* carriers, however, was significant ($p < 0.001$).

Only 11.7% of non-carriers reported a family history of ovarian cancer, compared to 16.1% of *BRCA1* carriers ($p = 0.39$) and 29.0% of *BRCA2* carriers ($p = 0.017$ for comparison to non-carriers). Similarly, non-carriers were less likely to report a family history of breast cancer (15.2% for non-carriers *versus* 22.6% for *BRCA1* carriers and 35.5% for *BRCA2* carriers). The difference between *BRCA2* carriers and the non-carriers was significant ($p = 0.011$).

Table 3 compares reproductive factors among carriers and non-carriers. After adjusting for possible confounders, there were no significant differences between the groups for age at menarche, ages at first and last live birth, or breastfeeding. There was also no difference in the percent of nulliparous women between carriers and non-carriers. However, parous *BRCA1* carriers reported fewer live births than parous non-carriers. The average number of live births among parous women was 2.5 among non-carriers, but only 2.1 among *BRCA1* carriers (OR = 0.61, 95%CI = 0.39–0.95, adjusted for age at diagnosis, tubal ligation and duration of OC use). Although parous *BRCA2* carriers also reported fewer live births than non-carriers, the difference between parous *BRCA2* carriers and non-carriers was not significant.

Interestingly, compared to non-carriers, *BRCA1* carriers were more likely to report having had a tubal ligation (25.0 *versus* 10.2%, OR = 3.67, 95%CI = 1.55–8.70 adjusted for age at diagnosis, number of live births and OC use). *BRCA2* carriers were less likely to report a history of tubal ligation compared to non-carriers, but the difference was not significant. However, the difference between *BRCA1* and *BRCA2* carriers was significant ($p < 0.05$). No differences in hysterectomy were found between carriers and non-carriers.

We compared additional characteristics of oral contraceptive use between carriers and non-carriers (Table 4). No significant differences were found in ever use of OCs or in duration of OC use. However, *BRCA1* carriers were likely to have begun using OCs at a later mean age than non-carriers (24.0 *versus* 23.2 years of age, OR = 1.15, 95%CI = 1.01–1.30 adjusted for age at diagnosis, number of live births, tubal ligation and OC duration). *BRCA1* carriers were also more likely to report recent use of OCs. The mean interval from last

Table 2. Characteristics of *BRCA1* and *BRCA2* carriers and non-carriers

	BRCA− (n = 147)	*BRCA1*+ (n = 64)		*BRCA2*+ (n = 31)	
Demographic characteristics					
Mean year of birth	1936 ± 12.8	**1941 ± 9.9**	**$p = 0.005$**	1932 ± 12.1	$p = 0.14$
Mean age at diagnosis (years)	57.5 ± 12.5	**51.2 ± 9.9**	**$p = 0.001$**	60.8 ± 11.3	$p = 0.20$
Mean body mass index (kg/m^2)	24.8 ± 5.6	25.1 ± 5.5	$p = 0.753$	25.8 ± 6.8	$p = 0.40$
Family history of ovarian cancer, n (%)	17 (11.7)	10 (16.1)	$p = 0.391$	**9 (29.0)**	**$p = 0.017$**
Family history of breast cancer, n (%)	22 (15.2)	14 (22.6)	$p = 0.200$	**11 (35.5)**	**$p = 0.011$**
Family history of ovarian or breast cancer, n (%)	26 (17.7)	16 (25.0)	$p = 0.223$	**11 (35.5)**	**$p = 0.030$**
Reproductive characteristics					
Mean age at menarche (years)	12.7 ± 1.4	12.6 ± 1.6	$p = 0.746$	12.3 ± 1.6	$p = 0.139$
Parous, n (%)	124 (84.4)	49 (76.6)	$p = 0.178$	29 (93.6)	$p = 0.196$
Mean number of livebirths[a]	2.5 ± 1.2	**2.1 ± 0.8**	$p = 0.027$	2.3 ± 0.9	$p = 0.508$
Mean age at first birth[a]	26.0 ± 4.7	26.6 ± 4.2	$p = 0.453$	27.1 ± 5.1	$p = 0.261$
Mean age at last birth[a]	31.3 ± 4.8	30.1 ± 4.3	$p = 0.159$	32.1 ± 5.4	$p = 0.388$
Mean time since first birth (years)[a]	32.7 ± 13.8	**26.9 ± 11.6**	$p = 0.012$	33.6 ± 11.8	$p = 0.747$
Mean time since last birth (years)[a]	27.4 ± 12.9	23.3 ± 11.7	$p = 0.061$	28.6 ± 11.0	$p = 0.646$
Breastfeeding, n (%)	47 (32.0)	22 (34.4)	$p = 0.732$	8 (25.8)	$p = 0.501$
Mean duration of breastfeeding (months)[a]	5.6 ± 16.2	6.5 ± 16.4	$p = 0.743$	6.8 ± 12.3	$p = 0.721$
Tubal Ligation, n (%)	15 (10.2)	**16 (25.0)**	**$p = 0.007$**	2 (6.5)	$p = 0.522$
Hysterectomy, n (%)	19 (12.9)	7 (10.9)	$p = 0.687$	6 (19.4)	$p = 0.353$
OC characteristics					
OC use, n (%)	58 (39.2)	**36 (56.3)**	**$p = 0.025$**	11 (35.5)	$p = 0.680$
Mean duration of use (years)[b]	5.1 ± 4.9	3.7 ± 3.6	$p = 0.163$	3.4 ± 5.2	$p = 0.294$
Mean age at first use[b]	23.2 ± 4.9	24.0 ± 5.3	$p = 0.425$	23.6 ± 6.2	$p = 0.801$
Mean time since last use (years)[b]	21.4 ± 9.1	19.6 ± 8.0	$p = 0.360$	23.8 ± 9.9	$p = 0.429$

Plus–minus values are means ± SD. *p*-values are for comparison of carriers to non-carriers.

Bolded entries are significant at $p < 0.05$.

Missing data are as follows: four subjects (2 BRCA−, 2 *BRCA1*+): family history of breast or ovarian cancers; 1 *BRCA2*+ subject: BMI; 1 BRCA−subject: age at first and last birth.

[a] Among women who had a live birth; [b] Among ever users.

Table 3. Adjusted ORs and 95% CIs for reproductive characteristics according to *BRCA1/2* carrier status

	BRCA− (n = 147)	*BRCA1/2*+ (all carriers combined) (n = 95)		*BRCA1*+ (n = 64)		*BRCA2*+ (n = 31)	
		Adj[a] OR	95% CI	Adj[a] OR	95% CI	Adj[a] OR	95% CI
Age at menarche	Referent	0.93	0.78–1.11	1.01	0.81–1.26	0.80	0.60–1.06
Parous[b]	Referent	0.89	0.42–1.87	0.67	0.29–1.52	2.50	0.54–11.68
Number of livebirths[b,d]	Referent	**0.70**	**0.49–0.99**	**0.61**	**0.39–0.95**	0.85	0.55–1.31
Age at first birth[d]	Referent	1.02	0.95–1.09	0.98	0.90–1.07	1.05	0.96–1.15
Age at last birth[d]	Referent	1.01	0.94–1.08	0.96	0.88–1.04	1.06	0.97–1.16
Time since first birth[d]	Referent	0.98	0.92–1.06	1.02	0.94–1.11	0.95	0.87–1.04
Time since last birth[d]	Referent	1.00	0.93–1.06	1.04	0.96–1.13	0.95	0.86–1.03
Breastfeed	Referent	1.09	0.61–1.97	1.36	0.68–2.73	0.70	0.28–1.72
Duration of breastfeeding[d]	Referent	1.02	0.99–1.04	1.01	0.98–1.04	1.02	0.99–1.05
Tubal ligation[c]	Referent	**2.32**	**1.06–5.11**	**3.67**	**1.55–8.70**	0.65	0.14–3.16
Hysterectomy	Referent	1.56	0.69–3.54	1.79	0.63–5.07	1.37	0.48–3.91

[a] Each row represents a separate model. All models were adjusted for age at diagnosis, number of live births (continuous variables) and OC use and history of tubal ligation (yes/no), except for those noted by ([b]), which were not adjusted for number of live births, and those noted by ([c]), which were not adjusted for tubal ligation. ORs in bold are significant at the $p < 0.05$ level.

[d] Among women who had a live birth.

use to diagnosis was 19.6 years for *BRCA1* carriers and 21.4 years for non-carriers (OR = 0.89, 95%CI = 0.79–0.99 adjusted for age at diagnosis, number of live births, tubal ligation and OC duration). The differences in age at first OC use or recent OC use between *BRCA2* carriers and non-carriers were not significant.

Table 4. Adjusted ORs and 95% CIs for OC use according to *BRCA1* and *BRCA2* carrier status

	BRCA– (n = 147)	*BRCA1/2+* (all carriers combined) (n = 95)		*BRCA1+* (n = 64)		*BRCA2+* (n = 31)	
		Adj[a] OR	95% CI	Adj[a] OR	95% CI	Adj[a] OR	95% CI
OC use	Referent	1.21	0.67–2.17	1.29	0.66–2.52	1.11	0.44–2.76
Duration of use (years)[b,c]	Referent	0.93	0.83–1.03	0.92	0.80–1.04	0.92	0.78–1.09
Age at first use[c]	Referent	1.11	0.99–1.24	**1.15**	**1.01–1.30**	0.96	0.80–1.16
Time since last use[c]	Referent	0.91	0.82–1.01	**0.89**	**0.79–0.99**	1.01	0.86–1.19

[a] Each row represents a separate model. Each model is adjusted for age at diagnosis, year of birth, number of live births, OC duration (continuous variables) and history of tubal ligation, except for that noted by ([b]), which was adjusted for OC duration. ORs in bold are significant at the $p < 0.05$ level.

[c] Among ever users.

Discussion

We pooled data on Jewish women with invasive ovarian cancer from four sources in order to determine whether there were differences in OC use, childbearing, breastfeeding and tubal ligation between *BRCA1/2* mutation carriers with invasive ovarian cancer and non-carriers with the disease.

We found no difference in the percent of nulliparous women between carriers and non-carriers, although parous *BRCA1* carriers had experienced fewer live births than non-carriers (2.1 *versus* 2.5). This suggests that the effect of bearing children is similar for both *BRCA1* carriers and non-carriers. It is possible that the earlier age at diagnosis among *BRCA1* carriers may partially explain fewer live births in that group. However, in our population-based case–control study [16], healthy controls with a mean age of 49.5 years had on average 2.8 live births. This suggests that the earlier age of diagnosis cannot fully explain the observed reduced parity. Moreover, our analyses showed a similar finding (fewer live births compared to non-carriers) for parous *BRCA2* carriers, despite that fact that compared with non-carriers and *BRCA1* carriers, *BRCA2* carriers had a later age at diagnosis. We are careful to note, however, that this result failed to reach statistical significance, possibly due to the small number of *BRCA2* carriers in our study.

With regards to breastfeeding, we found no differences between *BRCA1/2* carriers and non-carriers. Thus, the effect of breastfeeding on ovarian cancer risk appears to be similar for both carriers and non-carriers. Similarly, no difference between *BRCA1/2* carriers and non-carriers were found for ever having a hysterectomy, suggesting that the effect of hysterectomy on ovarian cancer risk does not differ between carriers and non-carriers.

We found that OC use also appeared to be similar for both carriers and non-carriers, confirming a previous report [9]. Although we did find a statistically significant difference in age at first use and recency of use between *BRCA1* carriers and non-carriers, these differences were small and may be due to chance. We failed to demonstrate a similar association between early OC use or recency of OC use for *BRCA2* carriers. Again, this may be due to differences in the effects of OC use in *BRCA2* carriers, or it may be due to the small number of *BRCA2* carriers in our study.

We further found that the protection associated with early OC use differed between *BRCA1* and *BRCA2*, although this difference may be due to the small number of *BRCA2* carriers. Notably, the direction of the ORs for the age and timing data among *BRCA2* carriers was opposite to that of the ORs for the *BRCA1* carriers, suggesting that the difference between the two groups may be real and not an artifact of sample size.

These results are in contrast to those of Modan *et al.* [10] who reported that the use of OC provided no protection to Israeli Jewish *BRCA1/2* carriers. While we cannot exclude the possibility that our finding is due to chance, we believe that there are differences between the two studies that may explain these disparate findings. In particular, the duration and frequency of use of OCs were far less in the Israeli population than in the population studied here. Moreover, there may be differences in OC formulations between the two populations. In addition, as discussed below, the differences between the study designs (case–control *versus* case-only) and our small sample size may account for the different findings.

Interestingly, *BRCA1* carriers were more likely to report having had a tubal ligation than non-carriers. Several studies have shown an association between tubal ligation and a reduction in ovarian cancer risk [8, 17–19], although the exact mechanism remains unknown. Our results suggest that if the procedure does protect against ovarian cancer, it may not provide the same degree of protection to *BRCA1* carriers. This finding is in contrast to those of Narod *et al.* [20] who report a

reduction in risk from tubal ligation among *BRCA1* carriers (OR = 0.39, 95%CI = 0.21–0.63, adjusted for OC use, parity, history of breast cancer and ethnic group). Data from that study were obtained from a database containing information on women from high-risk families in Canada, the United States and the United Kingdom. The differences between that study and the results presented here may be due to differences in study populations (high-risk women with any *BRCA1/2* mutation *versus* Ashkenazi Jewish women with one of three mutations), study design (matched case–control *versus* case-only), or chance. In particular, the *BRCA1* gene has over 850 known mutations, and it is unknown whether risk factors for ovarian cancer vary by mutation type. Confounding with other factors, such as family history of breast or ovarian cancer, may also explain our findings.

Care must be taken in interpreting our results. First, subjects were drawn from several sources. It is possible that the different study designs and data collection methods could have resulted in differences among the data sets that would affect our results. We note that while tests for heterogeneity between BRCA status and reproductive factors revealed no significant heterogeneity among subject source, it is possible that the tests may be underpowered in this instance because of the small sample size and the amount of stratification needed to perform the analyses. Therefore, such a test may not be very meaningful.

Second, we tested for a subset of mutations associated with ovarian cancer within a well-defined ethnic population. This raises the question of the generalizability of our results to the non-Jewish population or to women with other mutations.

Third, three of the four sources, which provided 80 subjects (33% of the data) for this study, tested for only the three mutations found in the Ashkenazim. Recently, Frank *et al.* [21] reported that among 322 Ashkenazi individuals who underwent full sequence analysis only after negative results from a three-mutation test, six (1.9%) carried a non-founder deleterious mutation. Therefore, we may have missed some mutations and classified some carriers as non-carriers, although in light of the Frank data, we would expect that number to be less than three. Moreover, the study providing the majority of cases [11] tested for most of the truncating mutations in *BRCA1* and *BRCA2* reported to date in addition to the three founder mutations analyzed here. No additional mutations were found. That is, no mutations (other than the three founder mutations) were identified among the subjects reported here. Therefore, the occurrence of carrier misclassification would likely be small. Assuming that this misclassification is non-differential with respect to the exposures we examined, it would bias our results towards the null value.

About 40% of the cases included in this study were interviewed more than one year after their diagnoses. Women with a *BRCA1* or *BRCA2* mutation may have improved survival compared to women with non-hereditary ovarian cancer [22]. Therefore, it is possible that mutation carriers would be over represented among those interviewed more than a year after diagnosis. Indeed, among those women interviewed more than one year after diagnosis, 43% were *BRCA1/2* mutation carriers; among women interviewed within one year of diagnosis, only 36% carried a mutation. However, this methodological issue would only impact our findings if OC use, parity, breastfeeding and/or tubal ligation affect prognosis.

An additional limitation of this study is the sample size, which limits the detectable differences in OC use, parity and other factors between carriers and non-carriers, and may explain some of our negative findings.

Finally, our choice of a case-only approach has limitations that may have affected our findings. In particular, the case-only design assumes independence between the genetic marker and the environmental exposure [15]. However, it is often difficult to make this assessment, even in a large-scale study [10]. Hence, in the absence of such evidence, as is the case here, point estimates and confidence intervals must be interpreted cautiously. In particular, if there is uncertainty about the assumption that OC use and parity are independent of carrier status among Jewish women, then it is possible that the estimates reported here are less precise than the data suggest [23]. The estimates may also be biased. Specifically, if there were a positive association between genotype and exposure in the underlying population, then the interaction OR above one would be biased towards one when compared to the ratio of relative risks that we are attempting to estimate. A case–control analysis would address these limitations. Unfortunately, because our data came from four sources with separate study designs, we lacked a valid control group to which we could compare the distribution of risk factors found among the different case groups. Moreover, because of the low prevalence of *BRCA1/2* mutations in the general population, it is unlikely that we would have had enough carriers in any control population to employ a standard interaction analysis.

In conclusion, our data suggest that in women with ovarian cancer, using oral contraceptives, bearing children and breastfeeding do not differ between women with and without a *BRCA1/2* mutation. While the data presented here confirm previous findings [9], they stand in contrast to those reported recently by Modan *et al.* [10] which suggested that OCs may not be protective in

women with a *BRCA1* or *BRCA2* mutation. Moreover, our results contradict the recent report that tubal ligation provides protection against ovarian cancer in *BRCA1* mutation carriers [20]. The disagreement between our study and these other studies on the protectiveness of OCs and tubal ligation indicate a substantial lack of clarity on how to counsel women at high risk for ovarian cancer.

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American Colllege of Surgeons Comission on Cancer Registry Data Standards (ROADS, FORDS)	Translation/Subheadings
Primary Site	Chicago: Northwestern University or Manhasset: North Shore University Hospital
DOB: date of birth	DOB: date of birth
Date Initial Diagnosis	Date Initial Dx
Tumor Marker 1: CA 125	Tumor Marker: CA 125
ICDO 2,3 Histology	Histology ICD-0
Tumor Grade	Differntiation/Grade
Pathological staging:FIGO	FIGO Stage (Ia-IV)
AJCC staging: TNM	Tumor, Nodes, Metastases (distant)
Surgery Date	Primary Treatment: surgery
Biopsy Date	Primary Treatment: biopsy
Tumor Size	Dimension Disease Prior to Surgery= upper abdominal and pelvis
Surgical Margins	All Gross Tumor Removed?
Residual Primary Tumor following Cancer-Directerd Surgery	Macro Residual at Primary Surgery:abdomen and pelvis
Name of Primary Surgeon	Type of Primary Surgeon
Text Fields: # of Remaining Nodules	# of Remaining Nodules after surgery
Date of Chemo	Date of Chemotherapy
Type of Chemo	Chemotherapy Given
Text Fields: Chemo Regimen if Recorded	Chemotherapy Regimen
Text fields: Recurrence/nature of	Recurrence/nature of
Text fields: Disease Response & Status After Primary Therapy Complete	Disease Response & Status After Primary Therapy Completed
Date of recurrence	Date Recurrence
Other recurrence	Other recurrence
Type of recurrence	Type recurrence
Treatment for recurrence	Treatment for Recurrence
Site of recurrence	Site of recurrence
2nd Chemo, type, date and regimen	Chemo for Recurrence
Survival Quality	Normal Activity; Symptomatic and Ambulatory; Ambulatory >50% of time, occas.needs assistance; Ambulatory <50%, nurse care required; Bedridden, may require hospitilization; not applicable/dead; Unknown or unspecified
Date of Last Contact	Date of Last Contact
Vital Status	Patient Status: alive or dead
Cancer Status	Cancer status at Last Contact: evidence or no evidence of ov.ca.
Date of Death	Date of Death
Autopsy Findings	Autopsy Findings: evidence or no evidence of ov.ca.