The Ovarian Cancer Association Consortium (OCAC)

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Ovarian Cancer Association Consortium
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NCI Emerging Consortia

Funds received in 2005-2006 for a planning meeting for the OCAC

THE OVARIAN CANCER RESEARCH FUND, INC.

OCRF - Kathryn Sladek Smith Award

$300,000 annually for 3 years

- Bi-annual meetings
- Genotyping
- Central data repository and administration

RATIONALE

Association studies of genetic polymorphisms require large numbers of subjects in order to have adequate power to identify low penetrance effects; but because of the relative rarity of ovarian cancer most ongoing studies include hundreds of subjects rather than the thousands that are needed.

Because of the large number of polymorphisms in the human genome (about 10 million), false-positive associations inevitably are more frequent than true-positive associations even when studies are conducted in a scientifically rigorous fashion.

RATIONALE

Epithelial ovarian cancer is comprised of several histological types, and it is possible that a given polymorphism may not affect the risk of all of these.

Epidemiological risk factor data should be considered in association studies to allow for examination of interactions between behavioral and genetic risk factors.

Leadership of the OCAC

Steering Committee

Methodologic Working Group

Biospecimen and Genotyping Working Group

Ovarian Cancer Association Consortium Investigators

1) Cambridge
2) USC
3) Duke
4) Australia
5) Mayo Clinic
6) University of Pittsburgh
7) Fred Hutchinson
8) Yale University
9) Stanford
10) Denmark MALOVA study
11) Harvard University
12) UC Irvine
13) Moffitt/Toronto
14) University College London
15) NCI/Poland
16) Germany
17) Pomeranian Poland
18) Hawaii

OCAC Web Portal
https://dceg.cancer.gov/ovarian/

- Calendar
- News
- Contact List
- Document Posting
- Project specific working group areas (Teamspaces)
- OCAC background info & minutes from all conferences

Aim #1 - To develop an ovarian cancer association consortium (OCAC) that is dedicated to working together to identify and validate common low penetrance ovarian cancer susceptibility polymorphisms.

- Meet annually in concert with the American Society of Human Genetics meeting.
- Annual spring meeting will be hosted by an OCAC member institution.

Subjects in the OCAC

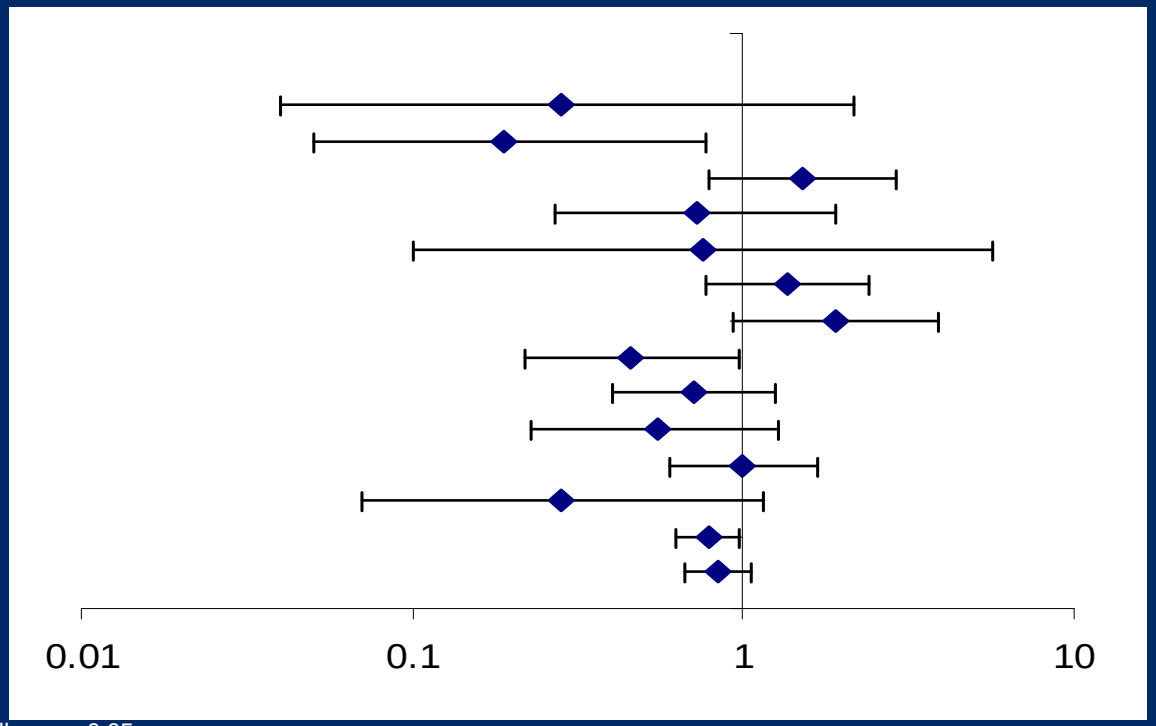
Location	DNA currently available			Projected		
	LMP	Invasive	Controls	LMP	Invasive	Controls
Australia	338	1328	1233	361	1371	1324
California (Stanford)	153	426	577	153	426	577
California (UCI)	250	633	640	300	700	700
California (USC)		885	1008		1700	1700
Cambridge, UK	130	970	1100	150	2000	2000
Connecticut		497	537		497	537
Denmark	170	504	1302	170	504	1302
Florida	20	212	232	75	675	750
Germany	30	225	430	30	225	430
Hawaii	55	290	616	60	319	705
London, UK	1	116	277		2000	4000
Massachusetts	180	1177	1202	256	1416	1701
Massachusetts	22	139	481	22	139	481
Minnesota	64	341	470	160	840	1000
North Carolina	203	718	980	256	800	1100
Pittsburgh		270	398		540	1080
Poland		603	603		603	603
Poland (NCI)		370	700		370	700
Washington	264	667	2486	315	857	2900
Total	**1,880**	**10,371**	**15,272**	**2,308**	**15,982**	**23,590**

Aim #2 – To perform a comprehensive review of the existing ovarian cancer susceptibility polymorphism literature.

- This effort will produce a review article and will serve as a marker of the state of the field as the OCAC begins its work.

Aim #3 – To determine whether polymorphisms in the progesterone receptor affect ovarian cancer risk.

- Polymorphisms in the progesterone receptor (PR) gene have been the most frequently examined, but there have been inconsistencies between studies.
- The OCAC members will genotype PR polymorphisms in several thousand cases and controls and the data will be analyzed centrally to resolve the issue of whether PR variants affect ovarian cancer risk.



Summary, $_{\text{all, } p_{het}<0.05}$ 0.79 (0.63-0.98, p=0.034)

Summary $_{\text{w/o NCOCS, } p_{het}<0.05}$ 0.84 (0.67-1.06, p=0.14)

Figure 1. Summary and stratified ORs and 95% CI for the +331 PGR SNP for invasive endometrioid/clear cell cases. Summary ORs are stratified on study and ethnicity.

Aim #4 – To examine associations between other promising candidate genetic variants and risk of ovarian cancer.

- In keeping with the goal of the OCAC to provide definitive evidence of genetic associations, the most promising candidate variants being studied by OCAC members will be genotyped in a collaborative manner.

Validation Gene List

PGR – 3 SNPs
RB-1 – 2 SNPs
CDKN2A – 1 SNP
BRCA2 – 1 SNP
CASP8 – 1 SNP
TGFB – 1 SNP
AURKA – 1 SNP
5-alpha reductase - 1 SNP

Aim #5 – To assign groups to write additional grant proposals that focus either on specific molecular pathways using a comprehensive approach or methodological issues for association studies.

- The groups in the OCAC are funded to study specific genes and/or gene pathways. The goal will be to assign groups to seek additional funding to study these pathways in the OCAC.

- The group will be uniquely positioned to study methodological issues related to genetic association studies and the statistical geneticists in the group will have the opportunity to apply for funding to use OCAC data for this purpose.

Aim #6 – To examine the interaction between major epidemiological risk factors and genetic polymorphisms.

- Because of the moderate size of most ovarian cancer association studies it has not been possible to perform analyses of gene-environment interactions.
- The OCAC will establish a common data sheet that includes basic information relating to major epidemiological risk factors.
- Central analyses will be performed to examine interactions between factors such as OC use, genetic polymorphisms and ovarian cancer risk.

Core Epidemiologic Data

The OCAC

Purpose

Control for potential confounding in data analysis

Subgroup analyses (histologic subtype, age, menopause status, parity, etc.)

Variable List

Study Site ID
Unique Subject ID
Case-control status
Race
Year of Birth
Year of Interview
Age
Pathologic Review (y/n)
Tumor Histology
Tumor Behavior

No. of full-term births
No. of pregnancies
Ever breast fed
Months of breastfeeding
Menopause status
Age at menopause
OC use
Months of OC use
Contraceptive patch
Months of patch use

Variable List

- Contraceptive ring
- Months of ring use
- Depo provera use
- Months of depo prevera use
- Norplant
- Months of norplant use
- Age at Menarche
- Age at end of last pregnancy
- Race of mother
- Race of father
- Usual adult weight
- Weight 1 year ago
- Weight in early adulthood
- Adult height
- Combination HRT use
- Months of HRT use
- Age 1st used HRT
- ERT use
- Months ERT use
- Age 1st used ERT
- 1º family hx of breast cancer

Variable List

1º family hx of ovarian cancer
Tubal ligation
Endometriosis
Hysterectomy
Age at hysterectomy

Compiled Data

To date: 10,216 cases and 12,433 controls (Australia, Cambridge UK, Germany, Hawaii, London UK, Massachusetts NHS & NECC, Minnesota, North Carolina, Pittsburgh, Poland, California-Stanford, California-UCI, California-USC)

More requests in progress: Connecticut, Florida, Washington

Tumor Characteristics

	Ovarian Cases n (%)
Tumor Behavior	
Borderline/LMP	1856 (19)
Invasive	7940 (81)
Don't know	420
Tumor Histology	
serous	5032 (56)
mucinous	1164 (13)
endometrioid	1097 (12)
clear cell	612 (7)
mixed cell	231 (3)
other specified epithelial ovarian cancer	491 (5)
undifferentiated/poorly differentiated epithelial	72 (1)
unknown, but epithelial	219 (2)
non-epithelial	9 (0)
unknown if epithelial	74 (1)
missing*	1215

*most are SEARCH which has not provided histology

Biospecimens and Genotyping Core Guidelines

- Corielle Test Plate
- Duplicate samples (≥3%)
- Negative controls
- Whole genome amplification
- Genotyping standards
- Hardy-Weinberg
- Appropriate technologies
- Questionnaire for all genotype uploads

OCAC

Meetings

2005

- Cambridge, England – April
- ASHG, Salt Lake City – October

2006

- Duke University, North Carolina April 23-25
- Dallas, TX October 6-8

- 2007
- London, April 28-29
- ASHG, San Diego October

Dallas, TX – October 2006