MOLECULAR ONCOLOGY 3 (2009) 171–181

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/molonc

Review

Role of genetic polymorphisms and ovarian cancer susceptibility

Peter A. Fasching[a,], Simon Gayther[b], Leigh Pearce[c], Joellen M. Schildkraut[d], Ellen Goode[e], Falk Thiel[f], Georgia Chenevix-Trench[g], Jenny Chang-Claude[h], Shan Wang-Gohrke[i], Susan Ramus[e], Paul Pharoah[j], Andrew Berchuck[k] for the OCAC (Ovarian Cancer Association Consortium)*

[a]*University of California at Los Angeles, David Geffen School of Medicine, Division of Hematology and Oncology, Los Angeles, CA, USA*
[b]*Translational Research Laboratory, University College London EGA Institute for Women's Health, London, United Kingdom*
[c]*University of Southern California, Keck School of Medicine, Los Angeles, CA, USA*
[d]*Department of Community and Family Medicine, Duke University Medical Center, Durham, NC, USA*
[e]*College of Medicine, Mayo Clinic, Rochester, MN, USA*
[f]*Department of Gynecology and Obstetrics, University Hospital Erlangen, Bavaria, Germany*
[g]*The Queensland Institute of Medical Research, Post Office Royal Brisbane Hospital, Australia*
[h]*Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany*
[i]*Department of Gynecology and Obstetrics, University Hospital Ulm, Germany*
[j]*Cancer Research United Kingdom, Department of Oncology, University of Cambridge, Strangeways Research Laboratory, Cambridge, United Kingdom*
[k]*Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC, USA*

ARTICLE INFO

Article history:
Received 1 January 2009
Accepted 28 January 2009
Available online 4 February 2009

Keywords:
Ovarian cancer
Risk
SNP
Genetic
Polymorphism
Early detection

ABSTRACT

The value of identifying women with an inherited predisposition to epithelial ovarian cancer has become readily apparent with the identification of the *BRCA1*, and *BRCA2* genes. Women who inherit a deleterious mutation in either of these genes have a very high lifetime risk of ovarian cancer (10–60%) and to some extent, increased risks of fallopian tube and peritoneal cancer. These highly lethal cancers are almost completely prevented by prophylactic salpingoophorectomy. *BRCA1/2* mutation testing has become the accepted standard of care in families with a strong history of breast and/or ovarian cancer. This approach has the potential to reduce ovarian cancer mortality by about 10%.

Although the ability to perform genetic testing for *BRCA1* and *2* represents a significant clinical advance, the frequency of mutations in these high penetrance ovarian cancer susceptibility genes is low in most populations. There is evidence to suggest that ovarian cancer susceptibility might be affected by common low penetrance genetic polymorphisms like it was shown for several common disorders like diabetes or breast cancer. Although such polymorphisms would increase risk to a lesser degree, they could contribute to the development of a greater proportion of ovarian cancers by virtue of their higher frequencies in the population. It has been shown that the most powerful approach to studying low penetrance genes is an association study rather than a linkage study design. This review describes the efforts that have been made in this field by individual case–control

* *Corresponding author.*
E-mail address: peter.fasching@uk-erlangen.de (P.A. Fasching).
1574-7891/$ – see front matter
doi:10.1016/j.molonc.2009.01.008

studies and through multi-center collaborations as part of international consortia such as the Ovarian Cancer Association Consortium (OCAC).

1. Need for lifetime risk assessment

Among gynecologic cancers, ovarian malignancies are the main reason of death in developed countries. Ovarian cancer is characterized by its high mortality, which is caused by its detection in advanced stages with a poor prognosis. Several obstacles to early detection of ovarian cancer exist, including its relative rarity, the occult location of the ovaries and the lack of a well defined pre-invasive lesion. However this makes ovarian cancer an ideal candidate to decrease mortality through improvements in early detection. Early stages have much better survival rates. Intensive efforts aimed at developing of a screening test are ongoing. In view of the relative rarity of ovarian cancer, the improvement in the specificity of a screening test would be most helpful to increase the positive predictive value (PPV) of the screening method. The PPV however depends on the absolute incidence within a screening population.

Therefore the identification of a subgroup of women, who are at higher risk for the disease may help to develop a strategy to improve ovarian cancer screening. Furthermore a more individualized primary prevention could be examined in these populations, such as the use of oral contraceptives and tubal ligation or possibly the use of NSAIDs.

2. Epidemiological risk factors

Several epidemiological and clinical risk factors are known to influence a women's lifetime risk for ovarian cancer. Reproductive behaviors and the use of hormonal therapies are the main clinical risk factors for ovarian cancer. Both pregnancy and use of oral contraceptives (OCs) dramatically reduce ovarian cancer incidence (Whittemore et al., 1992). Women who have three children or use OCs for more than 5 years have more than a 50% risk reduction. It is hypothesized that reductions in the numbers of lifetime ovulations due to pregnancy, OC use and breastfeeding may decrease the lifetime risk by reducing gonadotropin levels, oxidative stress, DNA replication errors and inclusion cyst formation in the ovarian epithelium. In addition, both pregnancy and OC use are characterized by a protective progestagenic hormonal milieu (Risch, 1998; Whittemore et al., 1992) and it has been suggested that this may reduce ovarian cancer risk by stimulating apoptosis of genetically damaged ovarian epithelial cells that might otherwise evolve into a fully transformed phenotype (Rodriguez et al., 2002, 1998). This may account for the observation that the protective effect of pregnancy and oral contraceptives is far greater than the extent to which lifetime ovulatory cycles are reduced (Whittemore et al., 1992). It has been suggested that a combination of oral contraceptives with high progestin potency are associated with a greater ovarian cancer risk reduction than those with low progestin potency (Pike et al., 2004; Schildkraut et al., 2002). Additional risk factors have been identified in addition to those that affect hormonal events and ovulation. Most notably, it has been shown that tubal ligation and hysterectomy reduce ovarian cancer risk by about 20–50% (Whittemore et al., 1992) perhaps by interrupting the access of perineal carcinogens such as talc to the ovary. In addition, endometriosis is associated with a 2–3 fold increased risk, particularly for clear cell and endometrioid cancers (Ness, 2003). Ovarian cancer incidence also has been noted to be higher in Northern regions with lower sunlight exposure (Lefkowitz and Garland, 1994). Finally, there is evidence that NSAIDs and other anti-inflammatory drugs may reduce ovarian cancer risk, as has also been noted for colon and breast cancer (Fairfield et al., 2002; Merritt et al., 2008).

3. High and low penetrance hereditary risk factors

In addition to these epidemiological factors a family history of ovarian cancer is another major risk factor that can contribute to the evaluation of a women's ovarian cancer lifetime risk. Population-based case–control studies have described a two to three-fold increased risk in first degree relatives of ovarian cancer patients. In principle, the familial aggregation of ovarian cancer may be the result of genetic or non-genetic factors that are shared within families. Twin studies which compare the concordance of ovarian cancer between monozygotic and dizygotic twins have shown that most of the excess familial risk of ovarian cancer is due to genetic factors (Lichtenstein et al., 2000). About 10% of invasive epithelial ovarian cancers are attributable to inherited mutations in high penetrance genes: *BRCA1* (3–6%), *BRCA2* (1–3%), HNPCC DNA mismatch repair genes (1–2%) (Berchuck et al., 1999; Frank et al., 1998). Most deleterious *BRCA* mutations encode truncated protein products, although missense mutations that alter a single amino acid in *BRCA1* or 2 have been found to segregate with disease in some of familial ovarian cancer clusters (Couch and Weber, 1996; Shattuck-Eidens et al., 1997). Inheritance of a *BRCA* mutation increases lifetime risk of ovarian cancer from a baseline of 1.5% to about 15–25% in *BRCA2* carriers and 20–40% in *BRCA1* carriers (Antoniou et al., 2003). Highly penetrant germline *BRCA* mutations are rare, however, and are carried by less than 1 in 500 individuals in most populations. There are some notable exceptions, particularly the of Ashkenazi Jews (1 carrier in 40 individuals) (Szabo and King, 1997). Even if the functional explanations, the testing opportunities and preventive options for *BRCA* mutation carriers are compelling, *BRCA* mutations are rare, and so the overall impact on mortality inevitably will be small.

Rare, high penetrance susceptibility alleles for many cancer types have been cloned by focusing on families with multiple and/or early onset cases. More recently, it has been shown that common, weakly penetrant alleles may exist that contribute to the burden of cancers that are often classified as sporadic

(i.e. without a heritable basis). Several million common genetic variants (polymorphisms) have been identified in the human genome (Cargill et al., 1999; Carlson et al., 2004; Sachidanandam et al., 2001; The International HapMap Project, 2003; Thorisson et al., 2005). The most common of these polymorphisms involves substitution of a single nucleotide (SNP). Many of these SNPs are either located outside of genes, with in introns or, if located in the coding sequence of genes, are frequently ''silent'' because they are not predicted to have a functional effect (i.e. they do not change the amino acid sequence). However, some SNPs that do change the amino acid code and may significantly alter the activity of a protein or its interactions with other molecules. SNPs that arise in introns or promoter regions may also conceivably alter the expression of the protein by affecting transcription.

4. Role of common genetic polymorphisms

Most genes contain numerous polymorphisms and current estimates suggest that there is on average one common SNP every 300 base pairs across the genome. The identification of common polymorphisms that predispose more weakly to cancer involves association studies in which the frequencies of SNP genotypes are compared between large population-based series of cases with age and population matched unaffected controls (Carlson et al., 2004; Risch and Merikangas, 1996). Although the extent of disease risks caused by these polymorphisms on risk is less striking than the one seen for seen BRCA mutations, however they can account for a larger fraction of ovarian cancer cases by virtue of their much higher prevalence in the population.

5. Selection strategies for polymorphisms in ovarian cancer studies

There are two approaches that one can take in performing genetic association studies – direct and indirect. In the direct approach putative functional variants, usually on selected candidate genes, are studied in the expectation that they are causally related to the disease of interest. Alternatively, the indirect approach takes advantage of the fact that polymorphisms in close physical proximity are often inherited together as a haplotype block. The elucidation of the haplotype structure surrounding genes of interest reduces the number of SNPs that need to be examined in each gene (http://www.hapmap.org/). Any one SNP tags the genetic information of all other tightly correlated SNPs because of the correlated nature of the SNPs (Thorisson et al., 2005). An extension of this tagging approach uses recently developed array based technologies that enable the rapid analysis of hundreds of thousands of tagged SNPs throughout the genome in case–control association studies, commonly referred to as genome-wide association study (GWAS).

The selection of candiate genes is an intentional, theory driven approach by analyzing candidate genes for which an a priori functional hypothesis is existent. These genes can be examined by analyzing all SNPs within the gene that have minor allele frequencies which are high enough to imply a clinical relevance (i.e. >5%). Furthermore multiple SNPs can be selected that describe in detail, the genetic variation within small areas of the human genome. Empirical studies have revealed block-like structures, and each block contains a set of haplotype tagging SNPs (htSNPs) which capture a large fraction of the haplotype diversity.

The second approach uses a non-intentional strategy which has been made possible through new technologies which examine several hundreds of thousand polymorphisms on array technology based platforms. These genome wide association studies (GWAS) are defined by the National Institutes of Health of the USA as studies of common genetic variations across the entire human genome designed to identify genetic associations with observable traits (National Institutes of Health, 2007). Both strategies have advantages and disadvantages. Testing polymorphisms in genes that are known to play a role in ovarian cancer pathogenesis or even treatment were thought to higher the probability for a finding that is relevant for explaining the risk for breast cancer. However these candidate gene studies are time and DNA consuming. Additionally many of the studies, which were based on the selection of candidate genes, failed to be confirmed in evaluation studies (Table 2). Genome wide association studies on the other hand are able to cover a large percentage of the whole genomic information. The newer SNP chips include up to a million SNPs. Using this approach however, which is cost intensive as well, the major challenge is to identify really true associations among many false positive associations. The GWAS approach also fails to provide much information about the functional, causal variants that are responsible for the variations in disease risk; SNP selection instead focuses on providing the greatest information possible on haplotype structure and genetic linkage to a disease phenotype.

6. Summary of recent studies on polymorphisms and ovarian cancer risk

Over the last few years several publications revealed an insight into theory driven research for polymorphisms that might contribute to ovarian cancer susceptibility. In this context genes that have a rationale for the involvement in ovarian cancer carcinogenesis have been analyzed. For example, it has been proposed that ovulation may increase ovarian cancer risk by increasing mutations in the epithelium that occur due to spontaneous errors in DNA synthesis or oxidative stress at the ovulatory site. It follows then, that SNPs in genes involved in DNA repair or metabolism of free radicals could affect ovarian cancer risk. Similarly, any increased risk of ovarian cancer associated with talc use and other exogenous carcinogens could be modified by genes that affect xenobiotic metabolism. It has been proposed that high levels of gonadotropins associated with ovulation may stimulate sex steroid hormone production, which in turn enhance proliferation and transformation in the ovarian epithelium. Thus, polymorphisms in the genes which regulate and facilitate these processes, such as gonadotropin releasing hormone, the androgen receptor and genes involved in sex steroid hormone biosynthesis and metabolism could affect ovarian cancer susceptibility. In addition, it is thought that the progestagenic

Table 1 – Summary of recent association studies for ovarian cancer.

Study (origin)	Gene(s)	No. of genes	No. of polymorphisms	Cases/ controls	Major finding	Year published	Ref
14 OCAC Studies (AUS (1), USA (8), DK (1), Poland (1), UK (2), GER (1))	AURKA, BRCA2, RB1, CDKN2A, SRD5A2, CASP8, TGFB1	7	7	4624/8113	RB1 and AURKA polymorphisms might be associated with OC risk	2008	Ramus et al., 2008
12 OCAC Studies (AUS (2), USA (7), DK (1), Poland (1), UK (1))	Progesterone receptor	1	3	4788/7614	No overall association, PROGINS polymorphism might contribute to endometrioid OC risk	2008	Pearce et al., 2008
SEARCH (UK), GEOCS (USA), MALOVA (DK), UKOPS (UK)	12 SNPs identified by a GWAS in a prostate cancer susceptibility study	12	12	2087/2491	rs2660743 on Chromosome 3 was associated with OC risk	2008	Song et al., 2008
MAYO (USA); DUKE (USA)	1-C transfer associated enzymes	21	180	829/941	SHMT1 minor allele increases OC risk, SHMT1 haplotype decreases OC risk	2008	Kelemen et al., 2008
MAYO (USA), DUKE (USA)	26 Genes with a glycosylation function	26	93	829/941	GALNT1 polymorphism was associated with OC risk	2008	Sellers et al., 2008
Hawaii (USA)	CYP19A1	1	2	367/602	Both polymorphisms showed an association with OC risk in at least one ethnic subgroup.	2008	Goodman et al., 2008
Hebei Study (North-East China)	CDKN2	1	2	205/268	Weak association with risk for serous OC	2008	Yan et al., 2008
Hebei Study (North-East China)	E-cadherin	1	3	207/256	One SNP associated with OC risk	2008	Li et al., 2008
Vienna Study (Austria)	Prohibitin	1	1	136/129	No association with OC risk	2007	Grimm et al., 2008
Sao Paolo, Brazil	Progesterone receptor	1	2 (PROGINS)	80/282	T2/T2 genotype associated with OC risk	2008	Leite et al., 2008
Auvergne Study, Central France	ERCC2	1	2	51/1000	Marginal significant association with OC risk	2008	Bernard-Gallon et al., 2008
Istanbul Study (Turkey)	MnSOD	1	1	55/51	No association with OC risk	2008	Dalan et al., 2008
Gilda Radner Familial Breast and Ovarian Cancer Registry (USA)	miR-146a	1	1	82 Cases only	Age at diagnosis associated with polymorphism in these OC patients with no BRCA mutation	2008	Shen et al., 2008
11 OCAC Studies (AUS (2), USA (6), DK (1), Poland (1), UK (1))	Cell cycle control genes CCND1, CCND2, CCND3, CCNE1, CDK2, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CDKN2D)	13	~88 SNPs in 3 studies as a first step-5 SNPs of the 88 in 8 evaluation studies	1500/2500 plus 2000/ 3200	One polymorphism in each of CDKN2A and CDKN1B were associated with OC risk	2007	Gayther et al., 2007

ACS (AUS), AOCS (AUS), MALOVA (DK), SEARCH (UK), GEOCS (USA)	SRD5A2, CYP19A1, HSB17B1, HSD17B4, XRCC2, XRCC3, BRCA2, RAD52	8	9	1466/1821 plus 1479/2452 for a SRDA2 evaluation	No associations except SRD5A2, within this gene inconsistent findings between AUS samples and validation samples (UK, USA; DK)	2007	Beesley et al., 2007
SEARCH (UK), MALOVA (DK), GEOCS (USA)	DNA repair gene BRIP1	1	12	Up to 3783/4795	Two SNPs showed marginal significant association with OC risk	2007	Song et al., 2007
Seoul National University (Korea)	MMP1	1	1	133/332	No association with OC risk	2007	Ju et al., 2007
Hereditary Cancer Registry (Poland)	Integrinβ3	1	1	146/290	Association with OC risk in BRCA1 mutated women.	2007	Jakubowska et al., 2007
SEARCH (UK), MALOVA (DK), GEOCS (USA)	**Mismatch repair genes** MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, PMS2	7	44	1531/2570	PMS2 polymorphisms might alter OC risk	2006	Song et al., 2006a
SEARCH (UK), MALOVA (DK), GEOCS (USA)	RB1	1	11	1481/4761	Two SNPs were associated with OC risk. Interaction with the P2RY5 gene suggested.	2006	Song et al., 2006b
Southern England (UK)	MDM2	1	1	302/258	No association with OC risk	2006	Campbell et al., 2006
Hebei Study (North-East China)	MMP1, MMP3, MMP7, MMP1	4	4	138/160	Weak association of MMP7 promoter polymorphism and OC risk	2006	Li et al., 2006
SEARCH (UK), MALOVA (DK), GEOCS (USA)	DNA repair genes (BRCA1, NBS1, RAF51, RAD52, XRCC2, XRCC3)	6	13	1600/4241	Some XRXX2 and XRCC3 polymorphisms were associated with OC risk	2005	Auranen et al., 2005
DUKE (USA)	TGFBR1	1	1	588/614	No association with OC risk	2005	Spillman et al., 2005
Hawaii (USA)	Calcitonin	1	1	182/219	Association with OC risk in women with Japanese origin	2005	Goodman et al., 2005
Southern England (UK)	FANCA	1	1	390/256	Weak association with OC risk, especially borderline cases	2005	Thompson et al., 2005
AOCS (AUS)	RAD52	1	1	508/298	No association with OC risk	2004	Kelemen et al., 2005
Thessaloniki (Greece)	p53	1	1	51/30	p53 polymorphism of codon 72 might be associated with OC risk	2004	Agorastos et al., 2004

milieu of pregnancy and OCs may have a protective effect by virtue of increasing apoptosis of ovarian epithelial cells that have undergone genetic damage, this then, makes the progesterone receptor or its downstream effectors good candidate susceptibility genes. Likewise, the relationship between low sunlight exposure and increased ovarian cancer risk could be attributable to vitamin D activity, and polymorphisms in genes involved in its action could be determinants of risk.

Table 1 gives an overview of the most recently (2004–2008) published studies: Pathways and genes that have been examined so far include genes of the estrogen and progesterone pathway and steroid hormone metabolism, double strand DNA repair genes, cell cycle genes, genes of the extracellular matrix and their degradading proteins, genes of cell segregation, tumor suppressor genes, apoptosis genes, growth factor genes, xenobiotic substances metabolizing genes, oncogenes, mismatch repair genes, genes involved in DNA synthesis and even a microRNA gene (for references see Table 1).

7. Polymorphisms involved in genes of the steroid hormone pathway or metabolism

Genetic polymorphisms of the progesterone receptor gene (*PGR*) are well described. A haplotype described as PROGINS (comprising of mainly three intronic and exonic polymorphisms in strong linkage disequilibrium) could be identified as a risk modifier for benign and malignant gynecologic diseases, indicating that this polymorphism affects the function of the progesterone receptor. In addition to polymorphisms in the exons and introns of the progesterone receptor gene, additional polymorphisms have been identified in the promoter region (De Vivo et al., 2002). The A allele of the +331SNP creates a unique transcriptional start site that favours the production of the progesterone receptor B (PR-B) isoform over progesterone receptor A isoform (PR-A) (De Vivo et al., 2002). The PR-A and PR-B isoforms are ligand-dependent members of the nuclear receptor family that are structurally identical except for an additional 164 amino acid at the N-terminus of PR-B, but their actions are distinct. The full length PR-B functions as a transcriptional activator and is a mediator of various responses, including the proliferative response to estrogen or the combination of estrogen and progesterone (Giangrande et al., 2000). PR-A is a transcriptionally inactive dominant-negative repressor of steroid hormone transcription activity that is thought to oppose estrogen-induced proliferation. An association has been reported between the +331A allele of the progesterone receptor promoter polymorphism and increased susceptibility to endometrial (De Vivo et al., 2002) and breast cancers (De Vivo et al., 2003). It was postulated that upregulation of PR-B in carriers of the +331A allele might enhance formation of these cancers due to an increased proliferative response.

For ovarian cancer three polymorphisms have been examined in a large multi-center case–control study as part of the Ovarian Cancer Association Consortium (OCAC) with more than 4700 cases and 7600 controls. The +331C/T promoter polymorphism, one of the PROGINS polymorphisms and a polymorphism in the 3′ UTR region of the gene have been examined (Pearce et al., 2008). In this analysis no strong association with ovarian cancer risk and these polymorphisms could be found. Only the PROGINS polymorphism was found to show evidence of association, but only for the endometriod subtype of ovarian cancer. Another report with a much lower sample size (80 cases and about 200 controls) found an association of a specific PROGINS haplotype to be associated with ovarian cancer risk.

Concerning further research in the sex hormone pathways, common polymorphisms in the *CYP19A1* gene have been examined, driven by the hypothesis, that these polymorphisms alter the function of the aromatase gene and thus the conversion of androgen to estrogen. Some of these polymorphisms have been associated with different peripheral sex hormone levels in postmenopausal women (Dunning et al., 2004; Haiman et al., 2007) and different survival outcomes in breast cancer patients (Fasching et al., 2008; Long et al., 2006). A Hawaiian study examined polymorphisms identified by Haiman et al., which alter estrogen level. One of these polymorphisms could be associated with ovarian cancer risk (rs749292) with some evidence (Goodman et al., 2008), however one SNP, which was previously described to alter peripheral sex hormone levels and to influence the outcome in breast cancer patients (rs10046), could not be associated with ovarian cancer risk in a large combined analysis of several case–control studies (Beesley et al., 2007).

Some effort has been put into the examination of several SNPs in the product of the steroid-5-a-reductase (*SRD5A2*) gene. SRD5A2 catalyses the conversion of testosterone to dihydrotestosterone, which might implicate its role in carcinogenesis through triggering polycystic ovaries by an androgenic pathway (Schildkraut et al., 1996). In an initial study, the rs523349 polymorphism within the *SRD5A2* gene was associated with a modified ovarian cancer risk. Another SNP, which is in linkage disequilibrium with rs523349 (rs632148) however showed no association with ovarian cancer risk (Beesley et al., 2007). Evaluating rs632148 in an even larger combined analysis of several case–control studies, this polymorphism could not be found to be associated with ovarian cancer risk (Ramus et al., 2008).

Some further polymorphisms of hormone pathway or metabolizing genes have been examined (*HSB17B1*, *HSD17B4*), however no association could be found with ovarian cancer risk.

8. Cell cycle control genes

Based on biological plausibility, genes, that regulate cell cycle are ideal candidate genes for being involved in carcinogenesis. Cell cycle is likely deregulated in cancer cells. Genes that are involved in the control of cell cycle are the cyclin-dependent kinases (*CDK*) and their coactivators and inhibitors, the cyclins and CDK inhibitors (Nam and Kim, 2008).

A study with 11 different case–control studies, that are part of the OCAC, examined 88 SNPs in 13 genes (4 cyclin genes, 3 CDK genes and 6 CDK inhibitors). The SNPs were selected to tag all the known common variants with a minor allele frequency $\geq$5% in order to tag most of unknown common variants. A two stage design was chosen for this analysis, with three studies from the UK, Denmark and California,

Table 2 – Comparison of initially significant associations between polymorphisms and ovarian cancer risk and their evaluation in larger case–control studies.

Gene	SNP	Original genotyping data				Follow-up genotyping			
		Cases	Controls	OR (95% CI)	P-value	Cases	Controls	OR (95% CI)	P-value
AURKA	rs2273535	1821	2467	**1.17 (1.02–1.35)**	**0.030**	2855	4963	1.05 (0.97–1.13)	0.254
BRCA2	rs144848	1121	2643	1.01 (0.87–1.18)	**0.030**	4174	7402	1.00 (0.94–1.06)	0.431
RB1	rs2854344	1500	4800	**0.73 (0.61–0.89)**	**0.0009**	3817	6584	**0.88 (0.79–1.00)**	**0.041**
SRD5A2	rs632148	1466	1821	**1.16 (1.00–1.36)**	**< 0.0001**	2982	5201	1.00 (0.93–1.07)	0.907
PGR	rs608995	267	397	**3.23 (1.63–5.89)**	**< 0.001**	4788	7614	1.05 (0.98–1.12)	0.2
PROGINS	rs1042838	267	397	**3.23 (1.19–8.75)**	**0.022**	4788	7614	1.04 (0.96–1.12)	0.33
CYP3A4	rs2740574	563	664	**2.83 (1.04–7.75)**	**0.043**	1969	3491	**2.73 (1.18–6.34)**	**0.019**
LIG4	rs1805386	1630	3986	**1.19 (1.05–1.35)**	**0.007**	3321	5140	1.00 (0.92–1.09)	0.97
XRCC2	rs3218536	2763	5479	0.89 (0.78–1.02)	0.095	5314	7673	0.95 (0.86–1.04)	0.28
CCND1	rs7178	1413	2431	**1.24 [1.03–1.49]**	**0.021**	3607	5725	1.09 [0.96–1.22]	0.12
CCND1	rs603965	1411	2403	1.06 [0.91–1.24]	0.010	3285	5236	1.02 [0.92–1.13]	0.084
CDK6	rs8	1409	2422	**1.18 [1.02–1.35]**	**0.0042**	3597	5720	**1.09 [1.00–1.19]**	0.082
CDKN1B	rs2066827	1416	2422	0.88 [0.77–1.01]	**0.0035**	3618	5719	0.98 [0.89–1.07]	**0.036**
CDKN2A/2B	rs3731257	1411	2415	0.90 [0.78–1.03]	**0.046**	3601	5705	**0.89 [0.81–0.97]**	**0.008**
NMI	rs11683487	1464	2564	**0.80 (0.69–0.93)**	**0.038**	2561	4356	**0.89 [0.80–0.99]**	**0.032**

USA, genotyping all 88 SNPs in a first step. In stage 2 additional 8 case–control studies (for countries of origin see Table 1) comprising 2000 cases and 3000 controls were genotyped for the 5 SNPs showing the most significant associations after stage 1. In the combined analysis of all 11 studies in each of the *CDKN2A* and *CDKN1B* genes there was one SNP which was found to be marginally associated with a decreased ovarian cancer risk (Gayther et al., 2007).

9. DNA repair and mismatch repair genes

The very strong association between *BRCA1*, *BRCA2*, and the HNPCC associated mismatch repair genes and high penetrance susceptibility to ovarian cancer underscores that DNA damage response pathways may be critical in the development of ovarian cancer. So far in several studies polymorphisms in these genes and others like *RAD51*, *RAD52*, *ERCC2*, *BRIP1*, *NBS1*, *XRCC2*. *XRCC3*, *MLH1*, *MLH3*, *MSH2*, *MSH3*, *MSH6*, *PMS1* and *PMS2* have been examined (for references see Table 1). Polymorphisms in genes associated with DNA damage response and the TP53 DNA damage checkpoint may also be important in the pathogenesis of ovarian cancer by affecting the frequency of TP53 overexpression and/or expression of TP53 associated genes (e.g. p21, *MDM2*, *ARF*, and *PIG3*). Genes involved in apoptosis also are appealing candidates, since failure to undergo cell death when DNA repair is not adequate may play a role in the development of some cancers.

A combined analysis of four large case–control trials (SEARCH, UK, MALOVA, Denmark, GEOCS, USA and RMH/YOC, UK) examined several DNA repair and mismatch repair genes (Table 1). With regard to DNA repair polymorphisms, SNPs in *XRCC2* and *XRCC3* showed a borderline association with ovarian cancer risk. The coding SNP in *XRCC2* (rs3218536) in exon 4 was associated with a decreased ovarian cancer risk and the two SNPs in *XRCC3* (rs1799794 and rs1799796), which are located in the 5′ UTR region and intron 5 were associated with a decreased risk for serous ovarian cancer (Auranen et al., 2005). For the mismatch repair genes (Table 1) 44 tagging SNPs, in 7 MMR genes were genotyped from three different case–control studies. There was no strong evidence that genetic variation in any of these genes was associated with variations in ovarian cancer risk (Song et al., 2006a).

10. Other pathways

In the largest case–control study so far, conducted by the OCAC, seven candidate SNPs from seven different genes were evaluated which have shown some significant association in previous other studies (Ramus et al., 2008). Together more than 4600 ovarian cancer cases and more than 8100 controls were genotyped. A polymorphism in the *RB1* gene (rs2854344), which is located in intron 17 within an open reading frame that encodes a G protein coupled receptor (*P2RY5*), was shown to be associated with a decreased risk for ovarian cancer with a marginal significance. There was also a suggestion that rs2273535 in the *AURKA* gene was associated with an increased risk for ovarian cancer. *AURKA* is a mitotic centrosomal protein kinase involved in the control of chromosome segregation during mitosis. All other SNPs within this study did not show a significant association with ovarian cancer risk suggesting that the previous findings which had warranted their selection in this consortium analysis were false positives.

Another study which should be mentioned, is an analysis of SNPs in genes that code for enzymes involved in one carbon (1-C) metabolism. Dysfunction of these enzymes can lead to chromosomal strand breaks and abnormal patterns of methylation (Kelemen et al., 2008). Within 21 genes that were theoretically implicated in ovarian cancer carcinogenesis the large number of 188 tagging SNPs were selected. In the overall analysis two SNPs in the *SHMT1* gene (serine hydroxymethyltransferase 1) could be associated with an increased ovarian cancer risk. This study also provided a measure of false positive reporting probabilities (FPRP) (Wacholder et al., 2004) in order to address the methological limitations of candidate gene association studies.

11. Methology limitations and future strategies

Almost all of the studies described above use a candidate gene approach to search for common low-moderate risk variants associated with ovarian cancer. Although these studies have revealed several possible genetic associations of borderline significance, the initial studies were limited by sample size and so statistical power to detect associations at very stringent levels of significance was small. It has required multi-centre collaborations to follow-up potential positive associations, and this has been the major role of the OCAC. These collaborations have shown that for most SNPs the initial evidence of association is likely to be false, or that the associations remaining positive after validation are weak effects (summarised in Table 2).

It is anticipated that genome wide approaches to genetic association studies will be more successful at identifying ovarian cancer risk alleles. The last 18 months have seen a plethora of reports of GWASs for several common diseases including type 1 and 2 diabetes, obesity, myocardial infarction, hypertension, asthma, Alzheimer's and Crohn's disease. GWASs have also been performed for some common cancers, notably breast, prostate and colorectal cancers. Mostly, these GWASs have been successful at identifying several highly significant associations for each disease, and in some cases follow-up fine mapping and functional studies have managed to suggest plausible genes and mechanisms for their involvement in disease aetiology.

Markers identified by these association studies are generally not the true causal variant(s), and there may be 10s or even hundreds of variants that are correlated with any given marker that has been found to be associated with disease. Any one of these markers could be the true, disease-causing, functional variant. Identifying the true causal variant is a complex and difficult task involving both genetic epidemiological approaches (fine mapping) and molecular studies. The benefits of fine mapping are two-fold. Firstly, fine mapping may enable more accurate risk prediction. Any disease marker could be used for risk prediction (functional causality is not required), but the risk conferred by the causal allele may be greater than that conferred by the marker if 'marker' and 'disease allele' are not perfectly correlated. Secondly, it is important from a biological perspective to understand causal mechanisms by which a given SNP affects disease risk. Unless the causal allele is known, these biological mechanisms would be very difficult to study, as functional studies are complex and expensive and it would not be possible to do them on all correlated markers. Fine mapping can be used to narrow down the list of potential functional variants to a much smaller number.

No GWAS for ovarian cancer has yet been published. However, there are known to be two ongoing ovarian cancer GWASs, one from the UK and one from the USA, which are planned for completion in 2009. Each GWAS is utilising several ovarian cancer case–control studies that are part of the OCAC, and will also use the power of the OCAC to follow-up positive hits to validate the initial findings. Both studies are using a staged design for the GWAS to optimise statistical power. In stage 1, more than 600,000 SNPs are being genotyped in approximately 2000 ovarian cancer cases in each study using the same microarray platform. Thus by the end of this stage, about 4000 cases will have been genotyped for the same series of SNPs. Significantly, this will provide sample power not only to detect highly significant genetic associations for ovarian cancer, but also to stratify cases according to other features of disease such as clinical heterogeneity and epidemiological risk factors, which may lead to the identification of subtype specific genetic associations. Each GWAS then plans to genotype thousands of the top associations emerging from the stage 1 analysis in second stage that includes several thousand additional cases and controls. Combined, these studies will have genotyped approximately 15,000 ovarian cancer cases and 16,000 controls by the time they are completed.

After all, the use for the patient and the translation of the obtained evidence into clinical practice may not be neglected. The general aim of genetic association studies is not only to get an insight into the carcinogenesis but also to individualize preventive medicine. The addition of genetic susceptibility markers to risk prediction models for ovarian cancer could help to improve the efficiency of early detection tests and possibly even of a screening program (Pharoah et al., 2008). The expected results from further studies and the growing understanding of this field will hopefully help to create a tool which could be integrated in a screening program or make early detection studies more feasible.

REFERENCES

Agorastos, T., Masouridou, S., Lambropoulos, A.F., Chrisafi, S., Miliaras, D., Pantazis, K., Constantinides, T.C., Kotsis, A., Bontis, I., 2004. P53 codon 72 polymorphism and correlation with ovarian and endometrial cancer in Greek women. Eur. J. Cancer Prev. 13, 277–280.

Antoniou, A., Pharoah, P.D., Narod, S., Risch, H.A., Eyfjord, J.E., Hopper, J.L., Loman, N., Olsson, H., Johannsson, O., Borg, A., Pasini, B., Radice, P., Manoukian, S., Eccles, D.M., Tang, N., Olah, E., Anton-Culver, H., Warner, E., Lubinski, J., Gronwald, J., Gorski, B., Tulinius, H., Thorlacius, S., Eerola, H., Nevanlinna, H., Syrjakoski, K., Kallioniemi, O.P., Thompson, D., Evans, C., Peto, J., Lalloo, F., Evans, D.G., Easton, D.F., 2003. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am. J. Hum. Genet. 72, 1117–1130.

Auranen, A., Song, H., Waterfall, C., Dicioccio, R.A., Kuschel, B., Kjaer, S.K., Hogdall, E., Hogdall, C., Stratton, J., Whittemore, A.S., Easton, D.F., Ponder, B.A., Novik, K.L., Dunning, A.M., Gayther, S., Pharoah, P.D., 2005. Polymorphisms in DNA repair genes and epithelial ovarian cancer risk. Int. J. Cancer 117, 611–618.

Beesley, J., Jordan, S.J., Spurdle, A.B., Song, H., Ramus, S.J., Kjaer, S.K., Hogdall, E., DiCioccio, R.A., McGuire, V., Whittemore, A.S., Gayther, S.A., Pharoah, P.D., Webb, P.M., Chenevix-Trench, G., 2007. Association between single-nucleotide polymorphisms in hormone metabolism and DNA repair genes and epithelial ovarian cancer: results from two Australian studies and an additional validation set. Cancer Epidemiol. Biomarkers Prev. 16, 2557–2565.

Berchuck, A., Schildkraut, J.M., Marks, J.R., Futreal, P.A., 1999. Managing hereditary ovarian cancer risk. Cancer 86, 2517–2524.

Bernard-Gallon, D., Bosviel, R., Delort, L., Fontana, L., Chamoux, A., Rabiau, N., Kwiatkowski, F., Chalabi, N., Satih, S., Bignon, Y.J., 2008. DNA repair gene ERCC2

polymorphisms and associations with breast and ovarian cancer risk. Mol. Cancer 7, 36.
Campbell, I.G., Eccles, D.M., Choong, D.Y., 2006. No association of the MDM2 SNP309 polymorphism with risk of breast or ovarian cancer. Cancer Lett. 240, 195–197.
Cargill, M., Altshuler, D., Ireland, J., Sklar, P., Ardlie, K., Patil, N., Shaw, N., Lane, C.R., Lim, E.P., Kalyanaraman, N., Nemesh, J., Ziaugra, L., Friedland, L., Rolfe, A., Warrington, J., Lipshutz, R., Daley, G.Q., Lander, E.S., 1999. Characterization of single-nucleotide polymorphisms in coding regions of human genes. Nat. Genet. 22, 231–238.
Carlson, C.S., Eberle, M.A., Kruglyak, L., Nickerson, D.A., 2004. Mapping complex disease loci in whole-genome association studies. Nature 429, 446–452.
Couch, F.J., Weber, B.L., 1996. Mutations and polymorphisms in the familial early-onset breast cancer (BRCA1) gene. Breast Cancer Information Core. Hum. Mutat. 8, 8–18.
Dalan, A.B., Ergen, A., Yilmaz, H., Karateke, A., Isbir, T., 2008. Manganese superoxide dismutase gene polymorphism, MnSOD plasma levels and risk of epithelial ovarian cancer. J. Obstet. Gynaecol. Res. 34, 878–884.
De Vivo, I., Hankinson, S.E., Colditz, G.A., Hunter, D.J., 2003. A functional polymorphism in the progesterone receptor gene is associated with an increase in breast cancer risk. Cancer Res. 63, 5236–5238.
De Vivo, I., Huggins, G.S., Hankinson, S.E., Lescault, P.J., Boezen, M., Colditz, G.A., Hunter, D.J., 2002. A functional polymorphism in the promoter of the progesterone receptor gene associated with endometrial cancer risk. Proc. Natl. Acad. Sci. U.S.A. 99, 12263–12268.
Dunning, A.M., Dowsett, M., Healey, C.S., Tee, L., Luben, R.N., Folkerd, E., Novik, K.L., Kelemen, L., Ogata, S., Pharoah, P.D., Easton, D.F., Day, N.E., Ponder, B.A., 2004. Polymorphisms associated with circulating sex hormone levels in postmenopausal women. J. Natl. Cancer Inst. 96, 936–945.
Fairfield, K.M., Hunter, D.J., Fuchs, C.S., Colditz, G.A., Hankinson, S.E., 2002. Aspirin, other NSAIDs, and ovarian cancer risk (United States). Cancer Causes Control 13, 535–542.
Fasching, P.A., Loehberg, C.R., Strissel, P.L., Lux, M.P., Bani, M.R., Schrauder, M., Geiler, S., Ringleff, K., Oeser, S., Weihbrecht, S., Schulz-Wendtland, R., Hartmann, A., Beckmann, M.W., Strick, R., 2008. Single nucleotide polymorphisms of the aromatase gene (CYP19A1), HER2/neu status, and prognosis in breast cancer patients. Breast Cancer Res. Treat. 112, 89–98.
Frank, T.S., Manley, S.A., Olopade, O.I., Cummings, S., Garber, J.E., Bernhardt, B., Antman, K., Russo, D., Wood, M.E., Mullineau, L., Isaacs, C., Peshkin, B., Buys, S., Venne, V., Rowley, P.T., Loader, S., Offit, K., Robson, M., Hampel, H., Brener, D., Winer, E.P., Clark, S., Weber, B., Strong, L.C., Thomas, A., et al., 1998. Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. J. Clin. Oncol. 16, 2417–2425.
Gayther, S.A., Song, H., Ramus, S.J., Kjaer, S.K., Whittemore, A.S., Quaye, L., Tyrer, J., Shadforth, D., Hogdall, E., Hogdall, C., Blaeker, J., DiCioccio, R., McGuire, V., Webb, P.M., Beesley, J., Green, A.C., Whiteman, D.C., Goodman, M.T., Lurie, G., Carney, M.E., Modugno, F., Ness, R.B., Edwards, R.P., Moysich, K.B., Goode, E.L., Couch, F.J., Cunningham, J.M., Sellers, T.A., Wu, A.H., Pike, M.C., Iversen, E.S., Marks, J.R., Garcia-Closas, M., Brinton, L., Lissowska, J., Peplonska, B., Easton, D.F., Jacobs, I., Ponder, B.A., Schildkraut, J., Pearce, C.L., Chenevix-Trench, G., Berchuck, A., Pharoah, P.D., 2007. Tagging single nucleotide polymorphisms in cell cycle control genes and susceptibility to invasive epithelial ovarian cancer. Cancer Res. 67, 3027–3035.
Giangrande, P.H., Kimbrel, E.A., Edwards, D.P., McDonnell, D.P., 2000. The opposing transcriptional activities of the two isoforms of the human progesterone receptor are due to differential cofactor binding. Mol. Cell. Biol. 20, 3102–3115.
Goodman, M.T., Ferrell, R., McDuffie, K., Thompson, P.J., Wilkens, L.R., Bushley, A.W., Tung, K.H., Carney, M.E., Ness, R.B., 2005. Calcitonin gene polymorphism CALCA-624 (T/C) and ovarian cancer. Environ. Mol. Mutagen. 46, 53–58.
Goodman, M.T., Lurie, G., Thompson, P.J., McDuffie, K.E., Carney, M.E., 2008. Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. Endocr. Relat. Cancer 15, 1055–1060.
Grimm, C., Polterauer, S., Zeillinger, R., Tempfer, C., Sliutz, G., Reinthaller, A., Hefler, L.A., 2008. The prohibitin 3′ untranslated region polymorphism in patients with ovarian cancer. Eur. J. Obstet. Gynecol. Reprod. Biol. 137, 236–239.
Haiman, C.A., Dossus, L., Setiawan, V.W., Stram, D.O., Dunning, A.M., Thomas, G., Thun, M.J., Albanes, D., Altshuler, D., Ardanaz, E., Boeing, H., Buring, J., Burtt, N., Calle, E.E., Chanock, S., Clavel-Chapelon, F., Colditz, G.A., Cox, D.G., Feigelson, H.S., Hankinson, S.E., Hayes, R.B., Henderson, B.E., Hirschhorn, J.N., Hoover, R., Hunter, D.J., Kaaks, R., Kolonel, L.N., Le Marchand, L., Lenner, P., Lund, E., Panico, S., Peeters, P.H., Pike, M.C., Riboli, E., Tjonneland, A., Travis, R., Trichopoulos, D., Wacholder, S., Ziegler, R.G., 2007. Genetic variation at the CYP19A1 locus predicts circulating estrogen levels but not breast cancer risk in postmenopausal women. Cancer Res. 67, 1893–1897.
Jakubowska, A., Gronwald, J., Menkiszak, J., Gorski, B., Huzarski, T., Byrski, T., Edler, L., Lubinski, J., Scott, R.J., Hamann, U., 2007. Integrin beta3 Leu33Pro polymorphism increases BRCA1-associated ovarian cancer risk. J. Med. Genet. 44, 408–411.
Ju, W., Kim, J.W., Park, N.H., Song, Y.S., Kim, S.C., Kang, S.B., Lee, H.P., 2007. Matrix metalloproteinase-1 promoter polymorphism and epithelial ovarian cancer: does ethnicity matter? J. Obstet. Gynaecol. Res. 33, 155–160.
Kelemen, L., Spurdle, A.B., Purdie, D.M., Gertig, D., Chenevix-Trench, G., 2005. RAD52 Y415X truncation polymorphism and epithelial ovarian cancer risk in Australian women. Cancer Lett. 218, 191–197.
Kelemen, L.E., Sellers, T.A., Schildkraut, J.M., Cunningham, J.M., Vierkant, R.A., Pankratz, V.S., Fredericksen, Z.S., Gadre, M.K., Rider, D.N., Liebow, M., Goode, E.L., 2008. Genetic variation in the one-carbon transfer pathway and ovarian cancer risk. Cancer Res. 68, 2498–2506.
Lefkowitz, E.S., Garland, C.F., 1994. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. Int. J. Epidemiol. 23, 1133–1136.
Leite, D.B., Junqueira, M.G., de Carvalho, C.V., Massad-Costa, A.M., Goncalves, W.J., Nicolau, S.M., Lopes, L.A., Baracat, E.C., da Silva, I.D., 2008. Progesterone receptor (PROGINS) polymorphism and the risk of ovarian cancer. Steroids 73, 676–680.
Li, Y., Jin, X., Kang, S., Wang, Y., Du, H., Zhang, J., Guo, W., Wang, N., Fang, S., 2006. Polymorphisms in the promoter regions of the matrix metalloproteinases-1, -3, -7, and -9 and the risk of epithelial ovarian cancer in China. Gynecol. Oncol. 101, 92–96.
Li, Y., Liang, J., Kang, S., Dong, Z., Wang, N., Xing, H., Zhou, R., Li, X., Zhao, X., 2008. E-cadherin gene polymorphisms and haplotype associated with the occurrence of epithelial ovarian cancer in Chinese. Gynecol. Oncol. 108, 409–414.
Lichtenstein, P., Holm, N.V., Verkasalo, P.K., Iliadou, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A., Hemminki, K., 2000.

Environmental and heritable factors in the causation of cancer – analyses of cohorts of twins from Sweden, Denmark, and Finland. N. Engl. J. Med. 343, 78–85.

Long, J.R., Kataoka, N., Shu, X.O., Wen, W., Gao, Y.T., Cai, Q., Zheng, W., 2006. Genetic polymorphisms of the CYP19A1 gene and breast cancer survival. Cancer Epidemiol. Biomarkers Prev. 15, 2115–2122.

Merritt, M.A., Green, A.C., Nagle, C.M., Webb, P.M., 2008. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. Int. J. Cancer 122, 170–176.

Nam, E.J., Kim, Y.T., 2008. Alteration of cell-cycle regulation in epithelial ovarian cancer. Int. J. Gynecol. Cancer.

National Institutes of Health, 2007. Policy for sharing of data obtained in NIH supported or conducted genome-wide association studies (GWAS). Fed. Regist. 72, 49290–49297.

Ness, R.B., 2003. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. Am. J. Obstet. Gynecol. 189, 280–294.

Pearce, C.L., Wu, A.H., Gayther, S.A., Bale, A.E., Beck, P.A., Beesley, J., Chanock, S., Cramer, D.W., DiCioccio, R., Edwards, R., Fredericksen, Z.S., Garcia-Closas, M., Goode, E.L., Green, A.C., Hartmann, L.C., Hogdall, E., Kjaer, S.K., Lissowska, J., McGuire, V., Modugno, F., Moysich, K., Ness, R.B., Ramus, S.J., Risch, H.A., Sellers, T.A., Song, H., Stram, D.O., Terry, K.L., Webb, P.M., Whiteman, D.C., Whittemore, A.S., Zheng, W., Pharoah, P.D., Chenevix-Trench, G., Pike, M.C., Schildkraut, J., Berchuck, A., 2008. Progesterone receptor variation and risk of ovarian cancer is limited to the invasive endometrioid subtype: results from the Ovarian Cancer Association Consortium pooled analysis. Br. J. Cancer 98, 282–288.

Pike, M.C., Pearce, C.L., Peters, R., Cozen, W., Wan, P., Wu, A.H., 2004. Hormonal factors and the risk of invasive ovarian cancer: a population-based case–control study. Fertil. Steril. 82, 186–195.

Pharoah, P.D., Antoniou, A.C., Easton, D.F., Ponder, B.A., 2008. Polygenes, risk prediction, and targeted prevention of breast cancer. N. Engl. J. Med 358, 2796–2803.

Ramus, S.J., Vierkant, R.A., Johnatty, S.E., Pike, M.C., Van Den Berg, D.J., Wu, A.H., Pearce, C.L., Menon, U., Gentry-Maharaj, A., Gayther, S.A., Dicioccio, R.A., McGuire, V., Whittemore, A.S., Song, H., Easton, D.F., Pharoah, P.D., Garcia-Closas, M., Chanock, S., Lissowska, J., Brinton, L., Terry, K.L., Cramer, D.W., Tworoger, S.S., Hankinson, S.E., Berchuck, A., Moorman, P.G., Schildkraut, J.M., Cunningham, J.M., Liebow, M., Kjaer, S.K., Hogdall, E., Hogdall, C., Blaakaer, J., Ness, R.B., Moysich, K.B., Edwards, R.P., Carney, M.E., Lurie, G., Goodman, M.T., Wang-Gohrke, S., Kropp, S., Chang-Claude, J., Webb, P.M., Chen, X., Beesley, J., Chenevix-Trench, G., Goode, E.L., 2008. Consortium analysis of 7 candidate SNPs for ovarian cancer. Int. J. Cancer 123, 380–388.

Risch, H.A., 1998. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J. Natl. Cancer Inst. 90, 1774–1786.

Risch, N., Merikangas, K., 1996. The future of genetic studies of complex human diseases. Science 273, 1516–1517.

Rodriguez, G.C., Nagarsheth, N.P., Lee, K.L., Bentley, R.C., Walmer, D.K., Cline, M., Whitaker, R.S., Isner, P., Berchuck, A., Dodge, R.K., Hughes, C.L., 2002. Progestin-induced apoptosis in the Macaque ovarian epithelium: differential regulation of transforming growth factor-beta. J. Natl. Cancer Inst. 94, 50–60.

Rodriguez, G.C., Walmer, D.K., Cline, M., Krigman, H., Lessey, B.A., Whitaker, R.S., Dodge, R., Hughes, C.L., 1998. Effect of progestin on the ovarian epithelium of macaques: cancer prevention through apoptosis? J. Soc. Gynecol. Investig. 5, 271–276.

Sachidanandam, R., Weissman, D., Schmidt, S.C., Kakol, J.M., Stein, L.D., Marth, G., Sherry, S., Mullikin, J.C., Mortimore, B.J., Willey, D.L., Hunt, S.E., Cole, C.G., Coggill, P.C., Rice, C.M., Ning, Z., Rogers, J., Bentley, D.R., Kwok, P.Y., Mardis, E.R., Yeh, R.T., Schultz, B., Cook, L., Davenport, R., Dante, M., Fulton, L., Hillier, L., Waterston, R.H., McPherson, J.D., Gilman, B., Schaffner, S., Van Etten, W.J., Reich, D., Higgins, J., Daly, M.J., Blumenstiel, B., Baldwin, J., Stange-Thomann, N., Zody, M.C., Linton, L., Lander, E.S., Altshuler, D., 2001. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. Nature 409, 928–933.

Schildkraut, J.M., Calingaert, B., Marchbanks, P.A., Moorman, P.G., Rodriguez, G.C., 2002. Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. J. Natl. Cancer Inst. 94, 32–38.

Schildkraut, J.M., Schwingl, P.J., Bastos, E., Evanoff, A., Hughes, C., 1996. Epithelial ovarian cancer risk among women with polycystic ovary syndrome. Obstet. Gynecol. 88, 554–559.

Sellers, T.A., Huang, Y., Cunningham, J., Goode, E.L., Sutphen, R., Vierkant, R.A., Kelemen, L.E., Fredericksen, Z.S., Liebow, M., Pankratz, V.S., Hartmann, L.C., Myer, J., Iversen Jr., E.S., Schildkraut, J.M., Phelan, C., 2008. Association of single nucleotide polymorphisms in glycosylation genes with risk of epithelial ovarian cancer. Cancer Epidemiol. Biomarkers Prev. 17, 397–404.

Shattuck-Eidens, D., Oliphant, A., McClure, M., McBride, C., Gupte, J., Rubano, T., Pruss, D., Tavtigian, S.V., Teng, D.H., Adey, N., Staebell, M., Gumpper, K., Lundstrom, R., Hulick, M., Kelly, M., Holmen, J., Lingenfelter, B., Manley, S., Fujimura, F., Luce, M., Ward, B., Cannon-Albright, L., Steele, L., Offit, K., Thomas, A., et al., 1997. BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. JAMA 278, 1242–1250.

Shen, J., Ambrosone, C.B., DiCioccio, R.A., Odunsi, K., Lele, S.B., Zhao, H., 2008. A functional polymorphism in the miR-146a gene and age of familial breast/ovarian cancer diagnosis. Carcinogenesis 29, 1963–1966.

Song, H., Koessler, T., Ahmed, S., Ramus, S.J., Kjaer, S.K., Dicioccio, R.A., Wozniak, E., Hogdall, E., Whittemore, A.S., McGuire, V., Ponder, B.A., Turnbull, C., Hines, S., Rahman, N., Eeles, R.A., Easton, D.F., Gayther, S.A., Dunning, A.M., Pharoah, P.D., 2008. Association study of prostate cancer susceptibility variants with risks of invasive ovarian, breast, and colorectal cancer. Cancer Res. 68, 8837–8842.

Song, H., Ramus, S.J., Kjaer, S.K., Hogdall, E., Dicioccio, R.A., Whittemore, A.S., McGuire, V., Hogdall, C., Jacobs, I.J., Easton, D.F., Ponder, B.A., Dunning, A.M., Gayther, S.A., Pharoah, P.D., 2007. Tagging single nucleotide polymorphisms in the BRIP1 gene and susceptibility to breast and ovarian cancer. PLoS ONE 2, e268.

Song, H., Ramus, S.J., Quaye, L., DiCioccio, R.A., Tyrer, J., Lomas, E., Shadforth, D., Hogdall, E., Hogdall, C., McGuire, V., Whittemore, A.S., Easton, D.F., Ponder, B.A., Kjaer, S.K., Pharoah, P.D., Gayther, S.A., 2006a. Common variants in mismatch repair genes and risk of invasive ovarian cancer. Carcinogenesis 27, 2235–2242.

Song, H., Ramus, S.J., Shadforth, D., Quaye, L., Kjaer, S.K., Dicioccio, R.A., Dunning, A.M., Hogdall, E., Hogdall, C., Whittemore, A.S., McGuire, V., Lesueur, F., Easton, D.F., Jacobs, I.J., Ponder, B.A., Gayther, S.A., Pharoah, P.D., 2006b. Common variants in RB1 gene and risk of invasive ovarian cancer. Cancer Res. 66, 10220–10226.

Spillman, M.A., Schildkraut, J.M., Halabi, S., Moorman, P., Calingaert, B., Bentley, R.C., Marks, J.R., Murphy, S., Berchuck, A., 2005. Transforming growth factor beta receptor I

polyalanine repeat polymorphism does not increase ovarian cancer risk. Gynecol. Oncol. 97, 543–549.
Szabo, C.I., King, M.C., 1997. Population genetics of BRCA1 and BRCA2. Am. J. Hum. Genet. 60, 1013–1020.
The International HapMap Project, 2003. The International HapMap Project. Nature 426, 789–796.
Thompson, E., Dragovic, R.L., Stephenson, S.A., Eccles, D.M., Campbell, I.G., Dobrovic, A., 2005. A novel duplication polymorphism in the FANCA promoter and its association with breast and ovarian cancer. BMC Cancer 5, 43.
Thorisson, G.A., Smith, A.V., Krishnan, L., Stein, L.D., 2005. The International HapMap Project web site. Genome Res. 15, 1592–1593.
Wacholder, S., Chanock, S., Garcia-Closas, M., El Ghormli, L., Rothman, N., 2004. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J. Natl. Cancer Inst. 96, 434–442.
Whittemore, A.S., Harris, R., Itnyre, J., 1992. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case–control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. Am. J. Epidemiol. 136, 1184–1203.
Yan, L., Na, W., Shan, K., Xiao-Wei, M., Wei, G., Shu-Cheng, C., 2008. p16(CDKN2) gene polymorphism: association with histologic subtypes of epithelial ovarian cancer in China. Int. J. Gynecol. Cancer 18, 30–35.