Role of Genetic Polymorphisms in Ovarian Cancer Susceptibility: Development of an International Ovarian Cancer Association Consortium

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The value of identifying women with an inherited predisposition to ovarian cancer has become readily apparent with the identification of the *BRCA1* and *BRCA2* genes. Women who inherit a deleterious mutation in one of these genes have a very high lifetime risk of ovarian cancer (10–60%) and lesser risks of fallopian tube and peritoneal cancer. These highly lethal cancers are almost completely prevented by prophylactic salpingoophorectomy. BRCA1/BRCA2 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 BRCA2 represents a significant clinical advance, the frequency of mutations in these high penetrance ovarian cancer susceptibility genes in the general population is low (about 1 in 500 individuals). There is evidence to suggest that ovarian cancer susceptibility is affected by low penetrance genetic polymorphisms that are much more common. Although such polymorphisms would increase risk to a lesser degree, they could contribute to the development of many ovarian cancers by virtue of their high frequency 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 (1). Several groups have obtained funding to initiate such studies and these generally have focused on polymorphisms in candidate genes purportedly involved in ovarian biology or carcinogenesis.

Over the last decade, initial reports from ovarian cancer association studies have been disappointing. Although numerous positive associations have been reported, in most cases these have not been confirmed by other groups. The accumulated experience to date has served to highlight how difficult it is to conduct statistically and methologically rigorous ovarian cancer association studies. The main issues are summarized below.

1. Association studies of genetic polymorphisms require large numbers of subjects to have adequate power to identify low penetrance effects; but because of the relative rarity of ovarian cancer, most studies include hundreds of subjects rather than the thousands that are needed.
2. Because of the large number of polymorphisms in the human genome (about 10 million), false-positive associations are inevitably more frequent than true-positive

G. Coukos et al. (eds.), *Ovarian Cancer*.

associations even when studies are conducted in a scientifically rigorous fashion. For example, using a significance level of 0.05, one false-positive result would be expected for every 20 polymorphisms examined.
3. Epithelial ovarian cancer is composed of several histological types that are somewhat heterogeneous with respect to predisposing risk factors and somatic mutations, and likewise it is possible that a given polymorphism may not affect the risk of all histologic types. The power of analyses stratified by histology is limited because of the smaller numbers of cases in each group.
4. Careful attention must be paid to issues of population stratification because both ovarian cancer rates and allele frequencies vary with race/ethnicity leaving open the possibility of residual confounding by race/ethnicity. This issue is one possible explanation for false-positive associations in the literature.
5. Epidemiological risk factor data should be considered in association studies to allow for examination of interactions between known etiologic factors (e.g., ovulation, endometriosis) and genetic risk factors. Because large samples sizes are needed to detect interactions, the power of these types of analyses in association studies has been extremely limited.

In view of the above-noted issues, over the last few years, collaborations have been initiated between groups in the US, UK, Europe, and Australia that are performing ovarian cancer association studies. To continue and expand this collaborative momentum, a meeting was held in Cambridge, England, in April 2005 to review the results of ongoing ovarian cancer association studies. The above-noted methodological issues that have slowed progress in the field were reviewed in detail. Presently, despite significant efforts by the various groups, little real progress has been achieved in understanding the contribution of genetic polymorphisms to ovarian cancer susceptibility. There was a consensus that many of the challenges inherent in this field can best be addressed by cooperative efforts. In view of this, the group unanimously decided to establish an ovarian cancer association consortium (OCAC). Shortly after the Cambridge meeting, an invitation to join the OCAC was extended to other groups known to be performing ovarian cancer association studies, and this was met with an enthusiastic response. Presently, 16 groups that are performing ovarian cancer case–control genetic association studies have joined the OCAC (Table 1). Together, over 10,000 cases and 15,000 controls have been accrued in these studies.

The work of the OCAC was funded in October 2005 by a generous donation from the family and friends of Kathryn Sladek Smith to the Ovarian Cancer Reseach Fund (www.ocrf.org). Biannual group meetings have been held for the past 2 years. The immediate goal of the group is to work together collaboratively to reach definitive results regarding polymorphisms that have been previously studied and to plan for future high quality studies. The development over time of a track record of collaboration and joint accomplishments will lay the groundwork for future studies, such as whole genome scans of thousands of polymorphisms.

Table 1 The Ovarian Cancer Association Consortium

United States
Duke University – North Carolina Ovarian Cancer Association Study
University of Southern California – Los Angeles Ovarian Cancer Association Study
University of Pittsburgh – HOPE (Hormones and Ovarian Cancer Prediction)
University of Washigton, Fred Hutchinson Cancer Institute – DOVE Study (Diseases of the Ovary and their Evaluation), OvCARE Study (Ovarian Cancer Contraceptive and Reproductive Experiences Study)
Mayo Clinic – Mayo Clinic Ovarian Cancer Association Study
Stanford University – San Francisco Bay Area Ovarian Cancer Genetic Epidemiology Study
Harvard University – New England Ovarian Cancer Case Control Study
Yale University – Connecticut Ovarian Cancer Study
University of California, Irvine – Orange County California Ovarian Cancer Study
University of South Florida, Moffitt Cancer Center – Tampa Bay Ovarian Cancer Study
University of Hawaii – Hawaii Ovarian Cancer Study
International
Cambridge University, UK – SEARCH East Anglian and West Midlands Study
University College London, UK – UK Ovarian Cancer Study
Queensland University, Australia – Australian Ovarian Cancer Study and Australian Cancer Study
Denmark – The Danish Malignant Ovarian Tumor study ("MALOVA")
NCI/Poland – Warsaw and Lodz Ovarian Cancer Study
Poland – West-Pomerania Region Hereditary Ovarian Cancer Study

1 Clinical Utility of Ovarian Cancer Susceptibility Polymorphisms

Although epidemiological risk factors for ovarian cancer have been identified, they are not sufficiently powerful to direct risk stratification in the clinic. Presently, ovarian cancer risk stratification is *not* used to guide clinical surveillance or interventions in the vast majority of women, other than in those rare individuals with mutations in the *BRCA* or *HNPCC* genes. The long-term goal of the OCAC is to identify a panel of ovarian cancer susceptibility polymorphisms that can be used in combination with known epidemiological risk factors such as family history, parity, and oral contraceptive use to better stratify ovarian cancer risk. We envision a future in which reduction of ovarian cancer incidence and mortality will be accomplished by implementation of screening and prevention interventions that focus on women defined as high risk, based on genetic and epidemiological risk factors. Such a focused approach likely will be more feasible and cost-effective than population-based approaches, given the relative rarity of ovarian cancer. Identifying genetic risk factors will also likely lead to improved understanding of the underlying biology and etiology of ovarian cancer and ultimately results in better ways of treating the disease.

Ovarian cancer is a highly lethal disease because most cases are detected at an advanced stage. 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 preinvasive lesion. Despite these challenges, intensive efforts aimed at the development of a screening test are ongoing. In addition to screening strategies, the protective effect of oral contraceptives, pregnancy, and NSAIDs against ovarian cancer provides evidence that risk reduction through preventive approaches may be possible. In view of the relative rarity of ovarian cancer, both screening and prevention approaches likely would be most cost effective if focused on populations at increased risk, based on epidemiological and genetic risk factors.

The next sections summarize the present understanding of the contributions of epidemiological risk factors and genetic susceptibility to ovarian cancer risk.

2 Epidemiology of Ovarian Cancer

In addition to genetic susceptibility, reproductive behaviors are the other main risk factors for ovarian cancer. Both pregnancy and use of oral contraceptives (OCs) dramatically reduce ovarian cancer incidence (2). Women who have three children or use OCs for more than 5 years have more than a 50% risk reduction. It is thought that reductions in numbers of lifetime ovulations due to pregnancy, OC use, and breastfeeding may decrease risk by reducing gonadotropin levels, oxidative stress, DNA replication errors, and inclusion cyst formation in the ovarian epithelium. In addition, both pregnancy and use of OC are characterized by a protective progestagenic hormonal milieu (2, 3), and it has been suggested that this may reduce ovarian cancer risk by stimulating apoptosis of genetically damaged ovarian epithelial cells that otherwise might eventually evolve a fully transformed phenotype (4, 5). This may account for the observation that the protective effect of pregnancy and OCs is far greater than the extent to which lifetime ovulatory cycles are reduced (2). It has been suggested that combination OCs with high progestin potency were associated with a greater ovarian cancer risk reduction than those with low progestin potency (6, 7).

Additional risk factors apart from those that affect hormonal events and ovulation have been identified. Most notably, it has been shown that tubal ligation and hysterectomy reduce ovarian cancer risk by about 20–50% (2), perhaps by interrupting the access of perineal carcinogens such as talc to the ovary. In addition, endometriosis is associated with a two to threefold increased risk, particularly for clear cell and endometrioid cancers (8). Ovarian cancer incidence also has been noted to be higher in Northern regions with lower sunlight exposure (9). Finally, there is evidence that NSAIDs and other antiinflammatory drugs reduce ovarian cancer risk, as has also been noted for colon and breast cancer (10).

3 Genetic Susceptibility

Population-based case–control studies have described a two to threefold 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 nongenetic factors that

are shared within families. Twin studies that 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 (11). 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%) (12, 13). Most deleterious BRCA mutations encode truncated protein products, although missense mutations that alter a single amino acid in BRCA1 or BRCA2 have been found to segregate with disease in a handful of familial ovarian cancer clusters (14, 15). 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 (16–18). Highly penetrant germline BRCA mutations are rare, however, and are carried by less than 1 in 500 individuals in most populations, with the notable exception of Ashkenazi Jews (1 in 40 carrier rate) (19). The ability to identify BRCA mutation carriers is an exciting advance, as these women can consider oophorectomy and other approaches aimed at decreasing ovarian cancer mortality (12, 20). On the other hand, because BRCA mutations are rare, the overall impact on mortality will be inevitably 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 hypothesized that common, weakly penetrant alleles may exist, which contribute to the burden of cancers classified as sporadic. Several million common genetic variants (polymorphisms) have been identified in the human genome (21–25). The most common of these polymorphisms involves substitution of a single nucleotide (SNP). Many of these SNPs are located either outside genes, in introns, or in the coding sequence of genes, and are "silent" because they do not alter the amino acid encoded. However, some SNPs that change a single amino acid may significantly alter the activity of a protein or its interactions with other molecules. SNPs that arise in introns or promoter regions may also alter expression of the protein by affecting transcription. In addition, insertion/deletion polymorphisms may occur in repetitive DNA sequences. Some trinucleotide repeats encode a stretch of a single amino acid, and variant alleles may alter the number of amino acid residues.

All genes have numerous polymorphisms, and current estimates suggest that on average there is one common SNP for every 300 bp across the genome. Identification of common polymorphisms that predispose more weakly to cancer involves association studies using groups of individuals with a given type of cancer and unaffected controls (1, 25). Although the potential effects of these polymorphisms on risk are less striking than seen with BRCA mutations, they could account for a larger fraction of ovarian cancer cases by virtue of their high prevalence. There are two approaches that can be taken to association studies – direct and indirect. In the direct approach, putative functional variants 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 physical proximity are often inherited together as a haplotype block. The elucidation of the haplotype structure of genes is facilitating association studies by reducing the number of SNPs that must be examined in each gene (http://www.hapmap.org/) because of the correlated nature of the SNPs.

4 Link Between Epidemiological and Genetic Risk Factors

Ovarian cancer risk is quite likely determined by a complex interaction between various inherited and acquired factors. 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. If so, polymorphisms 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 may enhance proliferation and transformation in the ovarian epithelium. Thus, polymorphisms in 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 milieu of pregnancy and OCs may have a protective effect by virtue of increasing apoptosis of ovarian epithelial cells that have undergone genetic damage. Thus, polymorphisms in the progesterone receptor or its downstream effectors could affect ovarian cancer risk. 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 a determinant of risk.

5 Review of Prior Ovarian Cancer Association Studies

Prior reports have examined the relationship between polymorphisms in several candidate genes and ovarian cancer risk. This includes the progesterone receptor (26–33), androgen receptor (34, 35), CYP17 (36, 37), p53 (38, 39), prohibitin (40), epoxide hydrolase (41, 42), BRCA1 and BRCA2 (43, 44), and others. Positive associations reported by some groups have not been confirmed by others, and this is attributable to chance; however, methodological weaknesses including using hospital- rather than population-based controls and employing controls that are poorly matched with respect to the presence of ovaries, age, and race (45). A few illustrative examples of some of these studies are described later.

5.1 Brca1/Brca2

Polymorphisms in *BRCA* genes are high priority ovarian cancer susceptibility candidates, since inactivation of these proteins strikingly increases ovarian cancer risk. Several members of the OCAC have examined common polymorphisms in BRCA1/

BRCA2. Initially, Ponder et al. reported that homozygosity for the H allele of the N372H polymorphism in *BRCA2* gene conferred a 1.3-fold increased risk of breast cancer (46). This is the only BRCA2 polymorphism with a rare allele frequency greater than 5% that results in an amino acid change. Dr. Chenevix-Trench examined N372H in UK and Australian ovarian cancer cases and controls and found a 1.7-fold increased risk (43). This polymorphism was also examined in the North Carolina Ovarian Cancer study, but no association was found between the H allele and risk of ovarian cancer (44). The overall odds ratio for HH homozygotes was 0.8 (95% CI = 0.4–1.5) and was similar in all subsets including invasive serous cases.

With regard to BRCA1, five amino acid changing polymorphisms have minor allele frequencies greater than 5% (Q356R, L871P, E1038g, K1183R, S1613G) (47). With the exception of Q356R, the others are highly correlated and only three haplotypes occur with a frequency of greater than 1.3% (48). In a population-based study of BRCA1 sequence variants in Southern California by Anton-Culver et al., the Q356R polymorphism was significantly associated with a family history among cases, suggesting that this polymorphism may influence risk (49). However, in the North Carolina Ovarian Cancer Study, neither the BRCA1 Q356R (OR = 0.9, 95% CI 0.5–1.4) nor P871L (OR = 0.9, 95% CI 0.6–1.9) polymorphisms were associated with ovarian cancer risk (44). A significant racial difference in allele frequencies was noted for the P871L polymorphism (P = 0.64 in Caucasians, L = 0.76 in African Americans, $p < 0.0001$).

5.2 Progesterone Receptor

In view of the protective effect of a progestin-dominant hormonal milieu (OC use, pregnancy), progesterone receptor variants with altered biological activity might affect ovarian cancer susceptibility. Polymorphisms in this gene have been studied in greater depth than those of any other gene, yet it remains unclear whether specific variants affect risk of ovarian cancer.

A German group reported that an insertion polymorphism in intron G of the progesterone receptor was associated with a 2.1-fold increased ovarian cancer risk (26, 27). It subsequently was shown that this intronic *Alu* insertion is in linkage disequilibrium with polymorphisms across the locus, including an amino acid changing SNP in exon 4 and a silent SNP in exon 5. However, several subsequent studies have failed to confirm an association between these polymorphisms and ovarian cancer risk (28–31). In addition, the evidence that this complex of polymorphisms, termed PROGINS, alters progesterone receptor function remains uncertain (50).

More recently, sequencing of the progesterone receptor gene by Pearce et al. at USC revealed the presence of four major haploytpe blocks within the gene (32). In this study, the association of PROGINS with ovarian cancer was explained by its cosegregation with the minor allele of the SNP rs608995. Homozygosity for the minor allele was seen in 4% of 387 controls compared with 11.2% of 267 cases (OR = 3.0; 95% CI = 1.63–5.89).

In addition to polymorphisms in the exons and introns of the progesterone receptor gene, additional polymorphisms have been identified in the promoter region (51). The A allele of the +331SNP creates an unique transcriptional start site that favors production of the progesterone receptor B (PR-B) isoform over progesterone receptor A (PR-A) (51). 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 acids at the N-terminus of PR-B, but their actions are distinct. The full length PR-B functions as a transcriptional activator and in the tissues where it is expressed, it is a mediator of various responses, including the proliferative response to estrogen or the combination of estrogen and progesterone (52). 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 (51) and breast cancers (53), although the breast cancer association has not been confirmed in two subsequent studies (32, 54). It was postulated that upregulation of PR-B in carriers of the +331A allele might enhance formation of these cancers because of an increased proliferative response.

Through collaborative efforts between two members of the OCAC (Duke and Australia), convincing evidence of association has been found between the +331A allele and ovarian cancer risk (33). Analyses involving the combined data set between these two studies showed a significant association between the +331A allele and decreased risk of endometrioid/clear cell cases (OR = 0.46, 95% CI = 0.23–0.92) (P = 0.027). The example underscores the importance of working together because the major finding is present among the less common endometrioid and clear cell subtypes of ovarian cancer that represent 21% of invasive cases. Endometriosis is known to increase risk of endometrioid and clear cell ovarian cancers, many of which may arise in ovarian deposits of endometriosis (8).

The literature is fraught with false-positive association studies of genetic susceptibility polymorphisms (25, 45), but several features mitigate the likelihood of this in the present study. First, the known protective benefit of progestins against ovarian cancer provides a preexisting biologic plausibility for the observed association. In addition, this collaborative effort showed a consistent effect across both the Duke and Australian study populations. Lastly, we have been able to combine the results from two additional OCAC members to provide further evidence of a true-positive association (Fig. 1). This is one of the first three variants that will be studied by the OCAC. Although the results appear convincingly positive, we cannot rule out publication bias as an issue for this association and therefore the combined efforts of the OCAC are necessary.

Finally, there is evidence to suggest that steroid hormones other than progesterone play a major role in ovarian carcinogenesis, both via affects on ovulation and direct effects on the ovarian epithelium. In view of this, polymorphisms in genes that comprise the estrogen, progesterone, androgen, and vitamin D receptor pathways also are high priority candidates

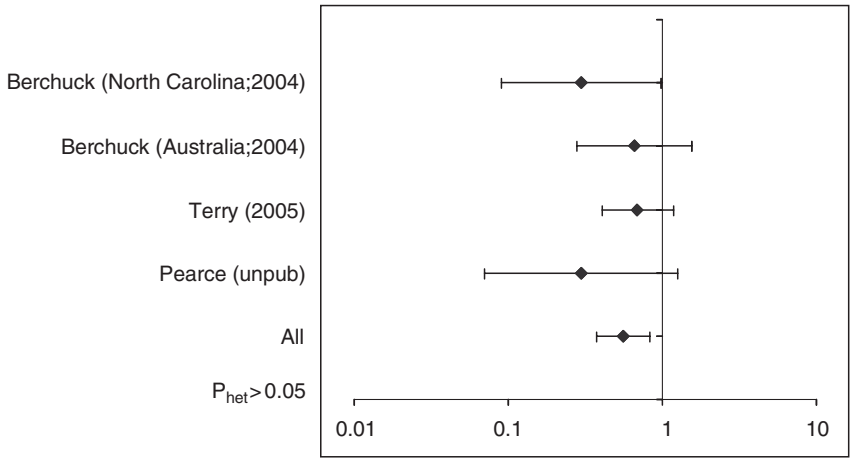

Fig. 1 Metaanalysis of the +331G/A progesterone receptor promoter polymorphism in endometrioid and clear cell ovarian cancers. The *X* axis represents the relative risk on a log scale. The *diamond* for each study represents the relative risk and the *error bar* the confidence intervals. A value of 1 indicates no association with values to the *right* representing increased risk and values to the *left* decreased risk. With all of the data combined there are 479 cases and 2,158 controls. The odds ratio for all of the data combined is 0.56 (95% CI 0.37–0.83)

5.3 DNA Repair Genes

The very strong association between mutated forms of *BRCA1*, *BRCA2*, and *HNPCC* mismatch repair genes and cancer underscores that DNA damage response pathways may be critical in the development of ovarian cancer. It is possible that variants in the genes that encode other proteins in the BRCA1 or BRCA2-associated complexes may adversely affect the efficiency of DNA repair and increase the risk of cancer, even if there are no high penetrance mutations in *BRCA1*, *BRCA2*, or *HNPCC* genes (e.g., *FANCD2*, *PMS2, BACH1, BARD1*, *GADD45*, *XPD, XRCC1*). In addition, polymorphisms associated with DNA damage response and the p53 DNA damage checkpoint may be important in the pathogenesis of ovarian cancer and affect the frequency of p53 overexpression and/or spectrum of p53 mutations (e.g., p*21, MDM2, ARF,* and *PIG3*). Genes involved in apoptosis also are appealing candidates, as failure to undergo cell death when DNA repair is not adequate may play a role in the development of some cancers.

5.4 Inflammation Pathways

Many of the established risk factors for ovarian cancer including ovulation and endometriosis have a link with inflammatory processes. Furthermore, it has been

shown that analgesic use is associated with decreased ovarian cancer risk. In view of this, polymorphisms in genes involved in inflammation pathways could affect ovarian cancer risk. This includes genes that encode cytokines or other molecules related to cytokine activity (e.g., TNF-α, IL-1β and IL-6, IL-1RA and IL-10). In addition, polymorphisms in genes involved in analgesic drug metabolism, drug effects (e.g., cyclooxygenases), and those that mediate the actions of arachidonic acid metabolites affect ovarian cancer risk (e.g., CYP2C9, CYP3A4, PTGS1, PTGS1) and could modify the protective effect of analgesics against ovarian cancer.

5.5 Other Pathways

Additional pathways to consider include those involved in methylation and acetylation of genes and chromatin remodeling as well as DNA replication and cell cycle regulation. Genes that regulate angiogenesis, invasion and metastasis, stromal–epithelial interactions, and those shown to be overexpressed in ovarian cancers using genomic approaches also represent appealing candidates.

6 Ovarian Cancer Association Consortium

6.1 Candidate Gene Approaches

The OCAC will work together to validate initial associations between single SNPs in candidate genes and ovarian cancer that are reported by individual groups. Data will be pooled for joint analyses. It is becoming increasingly desirable to study genes using a comprehensive approach to "rule out" the involvement of a given gene with a given phenotype (e.g., ovarian cancer). Taking this approach a step further, studies of complete biological pathways (e.g., DNA repair) involving multiple genes are being conducted at increasing frequency (55–57). In future, the OCAC will increasingly attempt to examine a set of SNPs that capture as completely as possible the underlying population variability within the chosen genetic loci. Although a locus or gene will contain many SNPs, a few "tag" SNPs can provide most of the information on its pattern of genetic variation such that all of the variation in the locus is marked by the tag SNPs. This is the principle of the indirect approach through which it is unnecessary to identify the "key" SNP in a gene as long as it is coinherited or in linkage disequilibrium (LD) with a representative genotyped SNP. The International HapMap Project (HapMap) was organized to provide extensive genotype data to the scientific community for the purposes of identifying disease associations (http://www.hapmap.org/) and this resource can be

used to select tag SNPs. We will select tag SNPs using standard methods (http://www.broad.mit.edu/mpg/tagger/) (58, 59).

There remain many important methodological issues to address in analyzing SNP data. For example, the optimal design strategy with regard to determining the number of samples that need to be genotyped is unclear in the context of preserving both financial and biological material resources. In addition, because both allele frequency and ovarian cancer rates vary by race/ethnicity, it will be important to consider the issue of population substructure among studies. In addition, the best way to explore the effect of multiple genes in a pathway is an area of active research (60).

The goal of genetic association studies is to determine whether a specific variant is associated with the risk of developing a given disease. However, the phenotypic expression of genetic variants is affected by environmental and behavioral factors. Information regarding known epidemiological risk factors should be incorporated into genetic association studies. For example, it is possible that the effect of certain polymorphisms on risk may only be manifest in women who are nulliparous or in those with a history of endometriosis. Because of the moderate size of most ovarian cancer association studies, it has not been possible for individual groups to perform meaningful analyses of gene–environment interactions. One of the aims of the consortium will be to establish a common data sheet that includes basic information relating to the major epidemiological risk factors. This will focus mainly on family history and reproductive risk factors. Analyses will be performed to examine interactions between specific risk factors, genetic polymorphisms, and ovarian cancer risk.

6.2 Whole Genome Studies

The discussion above focuses on association studies of polymorphisms in candidate genes that are selected based on a biological or epidemiological link to ovarian cancer. A potential pitfall of studies aimed at identification of ovarian cancer susceptibility polymorphisms using a candidate gene approach is the large number of polymorphisms in the genome. In addition, because our understanding of ovarian carcinogenesis is incomplete, many of the relevant genes may still be unidentified. An alternative strategy involves nonhypothesis-based high throughput approaches that examine thousands of polymorphisms across the genome to look for linkage. These whole genome approaches are arduous and generate many regions across the genome that must be studied further. Also, the optimal design for whole genome association scans is still an area of extensive debate. The infrastructure and working relationships established as the OCAC matures will lay the ground work for whole genome association studies in ovarian cancer.

Acknowledgments The Ovarian Cancer Association is funded by a generous donation from the family and friends of Kathryn Sladek Smith to the Ovarian Cancer Research Fund.

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