

Polymorphisms in the *FGF2* Gene and Risk of Serous Ovarian Cancer: Results From the Ovarian Cancer Association Consortium

Sharon E. Johnatty,¹ Jonathan Beesley,¹ Xiaoqing Chen,¹ Amanda B. Spurdle,¹ Anna DeFazio,³ Penelope M. Webb,¹ Australian Ovarian Cancer Study Group,^{1,3} Australian Cancer Study (Ovarian Cancer),¹ Ellen L. Goode,⁴ David N. Rider,⁴ Robert A. Vierkant,⁴ Stephanie Anderson,⁴ Anna H. Wu,⁵ Malcolm Pike,⁵ David Van Den Berg,⁶ Kirsten Moysich,⁷ Roberta Ness,⁸ Jennifer Doherty,⁹ Mary-Anne Rossing,⁹ Celeste Leigh Pearce,⁵ and Georgia Chenevix-Trench¹

¹ Queensland Institute of Medical Research, Brisbane, Queensland, Australia

² Department of Gynaecological Oncology and Westmead Institute for Cancer Research, University of Sydney at the Westmead Millennium Institute, Westmead Hospital, Sydney, Australia

³ Peter MacCallum Cancer Center, East Melbourne, Victoria, Australia

⁴ Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota, United States of America

⁵ Department of Preventive Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, United States of America

⁶ Department of Urology, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, United States of America

⁷ Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, New York, United States of America

⁸ The University of Texas School of Public Health, Houston, Texas, United States of America

⁹ Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA, United States of America

Fibroblast growth factor (*FGF*)-2 (basic) is a potent angiogenic molecule involved in tumor progression, and is one of several growth factors with a central role in ovarian carcinogenesis. We hypothesized that common single nucleotide polymorphisms (SNPs) in the *FGF2* gene may alter angiogenic potential and thereby susceptibility to ovarian cancer. We analyzed 25 *FGF2* tgSNPs using five independent study populations from the United States and Australia. Analysis was restricted to non-Hispanic White women with serous ovarian carcinoma (1269 cases and 2829 controls). There were no statistically significant associations between any *FGF2* SNPs and ovarian cancer risk. There were two nominally statistically significant associations between heterozygosity for two *FGF2* SNPs (rs308379 and rs308447; $p < .05$) and serous ovarian cancer risk in the combined dataset, but rare homozygous estimates did not achieve statistical significance, nor were they consistent with the log additive model of inheritance. Overall genetic variation in *FGF2* does not appear to play a role in susceptibility to ovarian cancer.

Keywords: ovarian cancer, serous, basic fibroblast growth factor, polymorphisms, *FGF2*

Ovarian cancer is the seventh leading cause of cancer mortality among women globally, accounting for 4.2% of cancer deaths (Parkin et al., 2005). Lethality of ovarian cancer is due in part to the absence of symptoms in the majority of cases who typically

present with metastatic disease that has spread outside the pelvis (Cannistra, 1993). The lack of practical screening methods and detectable symptoms in the early stages of tumor progression underscore the importance of a better understanding of the molecular aspects of disease to effective prevention and treatment (Wenham et al., 2002). Although the etiology of ovarian cancer has not been fully elucidated, it is generally agreed that family history of ovarian or breast cancer is the most important risk factor for epithelial ovarian cancer (Whittemore, 1994). Hereditary ovarian cancers occurring in breast/ovarian cancer families have been linked to mutations in the *BRCA1* and *BRCA2* genes, while cases occurring in association with Lynch syndrome have been linked to mutations in *MSH2* and *MLH1* (Boyd & Rubin, 1997; Pharoah & Ponder, 2002). Given that only 3–5% of cases present as high-risk familial cases (Wenham et al., 2002), it is plausible that several low-penetrance genes with relatively common alleles may account for a portion of the increased risk.

Fibroblast growth factor (*FGF*)-2 (basic) has been localized to 4q26-q27 and is a member of a large

Received 20 April, 2009; accepted 27 April, 2009.

Address for correspondence: G. Chenevix-Trench, Cancer and Cell Biology, Queensland Institute of Medical Research, c/o Royal Brisbane Hospital Post Office, Herston, QLD 4029, Australia. E-mail: georgiaT@qimr.edu.au

family of structurally related proteins that affect the growth and differentiation, migration and survival of a wide variety of cell types. It is highly conserved among eukaryotes with sequence homology of > 90% across a wide range of species (Bikfalvi et al., 1997). FGF2 is a potent angiogenic molecule and has been shown to induce migration and proliferation of endothelial cells which differentiate into new vascular structures (Folkman & Klagsbrun, 1987). Inactivation of FGF2 in vivo has been shown to suppress tumor growth through the inhibition of FGF2-induced angiogenesis (Hori et al., 1991). Elevated levels of urinary FGF2 were shown to correlate significantly with metastatic disease in a wide range of cancers including ovarian tumors (Nguyen et al., 1994). Expression studies in ovarian cancer cell lines have also demonstrated significant increases in mRNA expression of the FGF2 receptor, as well as dose-dependent increased cell numbers in response to exogenous stimulation by FGF2 (Crickard et al., 1994). In addition, gene expression profiling of advanced ovarian tumors indicates that FGF2 signalling plays a central role throughout the carcinogenesis process (De Cecco et al., 2004).

We hypothesized that common single nucleotide polymorphisms (SNPs) in the *FGF2* gene may alter the angiogenic potential of FGF2 and thereby susceptibility to ovarian cancer. While there is much evidence that *FGF2* is functionally relevant to tumor development and metastasis, to the best of our knowledge no study to date has assessed common variations in this gene for a possible association with ovarian cancer susceptibility. The current study evaluates 25 *FGF2* SNPs for an association with ovarian cancer risk, and represents a collaborative effort using data from five case-control studies from the United States and Australia, all participants in the Ovarian Cancer Association Consortium (OCAC; Gayther et al., 2000). OCAC is an international collaboration established to provide a forum for researchers to evaluate genetic associations with ovarian cancer with increased power.

Material and Methods

Study Population

Details of study design, and case and control ascertainment for each study included in this analysis are summarized in Table 1. A total of five ovarian cancer case-control studies contributed data to this analysis, four of which used population-based ascertainment methods and one (MAYO) that was clinic-based (Table 1). Individuals with missing data on tumor behavior, histology or race, and controls with prior oophorectomies, were excluded from the analysis. The final combined dataset comprised 1457 serous invasive cases and 3137 controls, the majority of whom were reported to be non-Hispanic Whites. All studies have been previously described elsewhere (Merritt et al., 2007; Pearce et al., 2008; Pike et al., 2004;

Rossing et al., 2007; Sellers et al., 2008). Approval from respective human research ethics committees was obtained, and all participants provided written informed consent.

Single Nucleotide Polymorphism Selection and Genotyping

Genotype data for this analysis was obtained from two 1536-SNP Illumina Golden Gate Assays™ conducted at two OCAC centers: AOCS-ACS and MAYO samples were genotyped at the Queensland Institute of Medical Research (QIMR), Queensland, Australia; DOVE, HOPE and USC samples were genotyped at the University of Southern California (USC) Epigenome Center, California, USA. Genotyping was conducted according to customized GoldenGate genotyping procedures (Illumina Inc.).

At QIMR we examined genotypes within 5 kb of *FGF2* (June 2006) from the projects of the HapMap Consortium ('The International HapMap Project', 2003), Perlegen (Hinds et al., 2005), NIEHS SNPs, and SeattleSNPs {http://pga.mbt.washington.edu/} and found HapMap to be the most informative for European-American samples using the binning algorithm of ldSelect (Carlson et al., 2004) to identify tagging SNPs (tgSNPs) for SNPs with $r^2 \geq 0.8$ and minor allele frequencies (MAFs) > 0.05. Fifty-eight SNPs were sorted into 20 bins, yielding 20 tgSNPs, 2 of which failed assay conversion. At USC we selected tgSNPs for *FGF2* (including putative regulatory regions 20kb up and 10kb downstream of the gene) using the program SNAGGER (Edlund et al., 2008). We attempted to tag all SNPs in HapMap (Release #21 July 2006) in the CEU population with a MAF of 0.05 or greater with an $r^2 \geq 0.8$.

A total of 25 *FGF2* SNPs were selected across both collaborations, 17 of which were genotyped for all studies, one was genotyped for the AOCS-ACS and MAYO studies only and seven were genotyped for DOVE, HOPE and UCS studies only (Table 2). The performance of our selected tgSNPs in capturing known common variation across the *FGF2* gene was evaluated using Tagger (de Bakker et al., 2005) implemented in Haploview (Barrett et al., 2005). We estimate that 97% of the known common variants (MAF ≥ 0.05) across the *FGF2* locus (including 20kb 5' and 10 kb 3' of the gene) have been captured by these SNPs.

Samples with call rates below 95% (or 90%), and SNPs with call rates below 98% (or 95%), were excluded at QIMR (and USC). At QIMR, SNPs with GenTrain scores < 0.5 were manually checked and adjusted according to Illumina guidelines; all SNPs were manually checked at USC. Greater than 97% and 93% of SNPs passed this initial quality assurance at QIMR and USC respectively. Two samples per 96 well plate were blindly duplicated ($n = 20$). One inter- and one intra-plate duplicate samples were included on each plate to assist with genotype calling and ensuring against plate flips. In addition, 128 blinded duplicate samples were included at USC. Genotyping quality was

Table 1

Description of Study Populations According to Contributing OCAC Study

Study(Location)	Case ascertainment	Cases				Control ascertainment	Controls	
		Total number ^a	Age ^b (Mean ± std. dev.)	Primary site ^d (ovary/tubal/primary peritoneal)	FIGO stage ^e (I/II/III/IV)		Total Number ^a	Age ^b (Mean ± std. dev.)
AOCS-ACS (Australia)	Surgical treatment centers throughout Australia, and cancer registries of Queensland, South and Western Australia, New South Wales and Victoria	549 (476)	60.4 (±10.1)	381/22/73	33/28/333/56	Population based: 1,028 (946) Commonwealth Electoral roll		57.4 (±11.6)
MAYO (USA)	Cases attending the Mayo Clinic from six surrounding states	124 (124)	*63.0 (±11.9)	124/0/0	8/3/85/27	Clinic based: Women seeking general exams at Mayo Clinic	60 (60)	*62.5 (±12.5)
DOVE (USA)	Cancer Surveillance System, SEER ^c	298 (274)	59.0 (±8.6)	298/0/0	n/a	Population based: Random digit dialling	726 (652)	55.9 (±9.5)
HOPE (USA)	Registries, physician offices, pathology databases	168 (161)	60.1 (±11.3)	168/0/0	n/a	Population based: Random digit dialling	702 (671)	57.6 (±10.3)
USC (USA)	Los Angeles Cancer Surveillance Program	318 (234)	59.3 (±10.9)	318/0/0	n/a	Population based: Neighbourhood recruits	621 (500)	55.7 (±12.9)
Totals	—	1457 (1269)	60.1 (±10.3)			—	3137 (2829)	56.9 (±11.2)

Note: ^a All serous invasive cases with genotype data available for analysis, with the number of non-Hispanic White in parentheses

^b Age of Non-Hispanic White serous cases (age at diagnosis) and controls (age at interview); mean and standard deviation based on total number; * no significant difference ($p \leq .05$) between mean age of cases and controls

^c SEER, Surveillance Epidemiology and End Results

^d Primary site of tumor among non-Hispanic White case (numbers may not sum to N because of missing data)

^e Stage of tumor among non-Hispanic White case (numbers may not sum to N because of missing data)

n/a – not available

also assessed using tests for Hardy-Weinberg equilibrium (HWE). SNPs with significant deviations from HWE in controls ($0.001 < P < .05$) were assessed and the genotype data was excluded if the clustering was found to be suboptimal. SNPs with HWE $P < .001$ were excluded from the analysis. Overall, > 84% and 91% of SNPs passed all quality assurance criteria at QIMR and USC, respectively.

Statistical Analysis

Case-control analyses were restricted to non-Hispanic White women with serous invasive ovarian tumors. White women participating in Australian studies were assumed to be non-Hispanic. Genotype frequencies in non-Hispanic White controls for each *FGF2* SNP were assessed for departure from HWE using the χ^2 goodness-of-fit test. Each of the five contributing case-control studies was assessed for differences in age at interview among controls and age at diagnosis among cases using Student's *t* test for comparison of means. The MAF for each SNP was estimated from the control population for each study.

The combined odds ratios (ORs) and their 95% confidence intervals (95% CIs) were obtained from

unconditional logistic regression models. Assuming a log additive model of inheritance, the per-allele risks associated with serous invasive tumors among non-Hispanic Whites for each of the 25 *FGF2* SNP were estimated by fitting the number of rare alleles carried as a continuous covariate. All estimates were adjusted for study site, and age at diagnosis for cases or age at interview for controls. All tests for association were two-tailed and statistical significance was assessed at $p < .05$ using STATA v. 9.0 (StataCorp, USA).

Results

Details of study design, and case and control ascertainment for each contributing study are summarized in Table 1. Genotype data across the different studies met the minimum quality assurance measure for inclusion in the analysis, with the exception of rs17473132 SNP, which was out of HWE in the USC study ($p = .0002$), resulting in the exclusion of 374 genotypes for this SNP from the final dataset. Cases were significantly more likely to be older than controls ($p < .0001$), and ranged in age at diagnosis from 23.6 to 86 years (mean age 60.1 ± 10.3) while controls ranged in age at interview

from 19.2 to 91 years (mean age 56.9 ± 11.2 ; see Table 1).

Estimates for the 25 *FGF2* SNPs and risk of invasive serous tumors were calculated among non-Hispanic White women, based on genotype data from a combined total of 1269 serous invasive cases and 2829 controls genotyped at both sites (Table 2). None of the 25 SNPs analyzed were significantly associated with risk of ovarian cancer although, without correcting for multiple testing, two SNPs showed borderline evidence of an association. The per-allele estimate for the rs308447 SNP showed a borderline significant inverse association with serous tumors [$OR_{\text{per-allele}} = 0.87$ (0.76 – 1.00), $p = .04$]. However, although the heterozygous estimate supports an association [$OR_{\text{Het}} = 0.72$ (0.59 – 0.87) $p = .001$], the odds ratio for rare homozygotes was neither statistically significant ($p > .4$) nor consistent with the log additive model of inheritance.

Similarly the rs308379 SNP was inversely associated with serous tumors among heterozygotes [$OR_{\text{Het}} = 0.85$ (0.74 – 0.98) $p = 0.03$] but no equivalent association was observed among rare homozygotes ($p = 0.59$), nor were the estimates consistent with the log additive model of inheritance (Table 2). These observations are likely to be due to chance alone, and we therefore conclude that there is no association between any of these 25 SNPs in *FGF2* and risk of invasive serous ovarian cancer in non-Hispanic White women.

Discussion

FGF2 is a potent angiogenic molecule that has been shown to promote tumor cell mitosis and has been implicated in the differentiation of stromal and epithelial cells from a dormant to an invasive phenotype (Dow et al., 2000). We have evaluated the effects of 25 SNPs in the *FGF2* gene on the risk of invasive

Table 2

Risk Estimates for the 25 *FGF2* SNPs Among Non-Hispanic White Women with Serous Carcinoma

SNP ^{id}	MAF ^a Controls/Cases ^b			Heterozygotes			Rare Homozygotes				Per-Allele				
	MAF ^a	Controls	Cases ^b	OR ^c	95% CI	P value	OR ^c	95% CI	P value	OR ^c	95% CI	P value	OR ^c	95% CI	P value
rs10003827 ^d	0.14	1,823	667	0.82	(0.66 – 1.02)	0.08	1.00	(0.52 – 1.92)	0.99	0.87	(0.72 – 1.05)	0.14	0.87	(0.72 – 1.05)	0.14
rs10452197	0.14	2,816	1,265	0.99	(0.84 – 1.16)	0.87	1.37	(0.88 – 2.13)	0.16	1.04	(0.91 – 1.19)	0.55	1.04	(0.91 – 1.19)	0.55
rs11737764 ^d	0.09	1,821	668	1.15	(0.91 – 1.45)	0.24	0.82	(0.30 – 2.26)	0.71	1.10	(0.89 – 1.36)	0.37	1.10	(0.89 – 1.36)	0.37
rs11938826	0.16	2,818	1,256	0.95	(0.81 – 1.11)	0.49	0.82	(0.53 – 1.29)	0.39	0.94	(0.82 – 1.07)	0.32	0.94	(0.82 – 1.07)	0.32
rs12506776	0.17	2,823	1,266	0.91	(0.78 – 1.06)	0.25	0.93	(0.63 – 1.38)	0.71	0.93	(0.82 – 1.06)	0.27	0.93	(0.82 – 1.06)	0.27
rs1476214	0.38	2,821	1,267	0.95	(0.82 – 1.09)	0.45	0.90	(0.73 – 1.10)	0.29	0.95	(0.86 – 1.04)	0.26	0.95	(0.86 – 1.04)	0.26
rs1476217 ^d	0.37	1,822	669	0.84	(0.69 – 1.02)	0.08	0.88	(0.67 – 1.15)	0.35	0.91	(0.80 – 1.04)	0.16	0.91	(0.80 – 1.04)	0.16
rs167428	0.27	2,826	1,267	1.03	(0.90 – 1.19)	0.64	0.94	(0.72 – 1.22)	0.63	1.00	(0.90 – 1.11)	0.96	1.00	(0.90 – 1.11)	0.96
rs17407577	0.06	2,828	1,269	0.89	(0.72 – 1.10)	0.29	2.63	(0.80 – 8.67)	0.11	0.95	(0.78 – 1.16)	0.61	0.95	(0.78 – 1.16)	0.61
rs17473132	0.07	2,536	1,159	1.20	(0.98 – 1.46)	0.08	0.18	(0.02 – 1.40)	0.10	1.11	(0.92 – 1.35)	0.26	1.11	(0.92 – 1.35)	0.26
rs1960669	0.14	2,825	1,267	0.93	(0.79 – 1.09)	0.39	1.16	(0.72 – 1.88)	0.53	0.97	(0.85 – 1.12)	0.69	0.97	(0.85 – 1.12)	0.69
rs308379	0.39	2,825	1,268	0.85	(0.74 – 0.98)	0.03	0.94	(0.77 – 1.16)	0.59	0.94	(0.85 – 1.04)	0.22	0.94	(0.85 – 1.04)	0.22
rs308382	0.16	2,822	1,269	0.92	(0.78 – 1.07)	0.26	1.18	(0.78 – 1.77)	0.43	0.97	(0.85 – 1.10)	0.63	0.97	(0.85 – 1.10)	0.63
rs308420	0.09	2,819	1,265	0.97	(0.81 – 1.17)	0.76	1.43	(0.71 – 2.89)	0.32	1.01	(0.86 – 1.20)	0.89	1.01	(0.86 – 1.20)	0.89
rs308428	0.14	2,826	1,268	0.99	(0.84 – 1.15)	0.86	0.95	(0.58 – 1.54)	0.82	0.98	(0.86 – 1.13)	0.80	0.98	(0.86 – 1.13)	0.80
rs308435 ^d	0.15	1,822	669	0.87	(0.71 – 1.07)	0.20	1.14	(0.68 – 1.93)	0.62	0.94	(0.79 – 1.11)	0.46	0.94	(0.79 – 1.11)	0.46
rs308439	0.04	2,805	1,256	0.97	(0.76 – 1.24)	0.83	na	na	na	0.92	(0.73 – 1.17)	0.51	0.92	(0.73 – 1.17)	0.51
rs308441	0.20	2,821	1,266	1.03	(0.89 – 1.19)	0.69	0.93	(0.65 – 1.33)	0.70	1.00	(0.89 – 1.13)	0.94	1.00	(0.89 – 1.13)	0.94
rs308443	0.03	2,823	1,266	0.96	(0.71 – 1.28)	0.77	na	na	na	0.91	(0.68 – 1.21)	0.51	0.91	(0.68 – 1.21)	0.51
rs308447 ^d	0.38	1,819	667	0.72	(0.59 – 0.87)	0.001	0.88	(0.67 – 1.16)	0.37	0.87	(0.76 – 1.00)	0.04	0.87	(0.76 – 1.00)	0.04
rs3789138 ^e	0.42	996	598	1.13	(0.89 – 1.42)	0.32	0.89	(0.65 – 1.21)	0.44	0.97	(0.84 – 1.13)	0.70	0.97	(0.84 – 1.13)	0.70
rs3804158	0.45	2,819	1,255	1.01	(0.86 – 1.18)	0.92	0.92	(0.76 – 1.11)	0.37	0.96	(0.88 – 1.06)	0.42	0.96	(0.88 – 1.06)	0.42
rs6819187 ^d	0.44	1,821	667	0.89	(0.73 – 1.09)	0.27	0.92	(0.71 – 1.19)	0.51	0.95	(0.84 – 1.08)	0.42	0.95	(0.84 – 1.08)	0.42
rs7694627 ^d	0.17	1,823	669	0.97	(0.79 – 1.18)	0.76	1.01	(0.59 – 1.74)	0.96	0.98	(0.83 – 1.16)	0.83	0.98	(0.83 – 1.16)	0.83
rs7700205	0.17	2,825	1,268	1.03	(0.89 – 1.19)	0.72	1.05	(0.71 – 1.54)	0.81	1.03	(0.91 – 1.16)	0.69	1.03	(0.91 – 1.16)	0.69

Note: 'na' represents SNPs with insufficient homozygote numbers for calculation of risk estimates; bold indicates $p < .05$

^a Minor allele frequency estimated from control population

^b Sample sizes reflect differences in genotype data available for analysis and exclusions based on HWE threshold

^c Odds Ratios (ORs) are adjusted for study and age (at interview for controls; at diagnosis for cases). Reference genotypes for case-control comparisons are common homozygotes

^d Indicates SNPs genotyped for DOVE, HOPE and USC studies only

^e Indicates SNPs genotyped for AOCs-ACS study only

serous ovarian cancer in non-Hispanic White women enrolled in five case-control studies from the United States and Australia, and found no convincing evidence of an association of any *FGF2* SNPs with serous ovarian tumors in our combined dataset. We acknowledge that the potential for variation in estimates is inherent in analyses involving samples from different countries, given the likelihood of differences in case-control selection criteria and population differences attributable to environmental factors or genetic background. However, all contributing studies included in our analysis selected controls from the same source population as cases, participants were predominantly non-Hispanic White (Table 1), and indeed there was no evidence of heterogeneity between the studies (non-Hispanic Whites only) for any of the SNPs included in this analysis ($P_{\text{Heterogeneity}} \geq .14$).

The human *FGF2* gene encompasses 71.53 kb of genomic sequences on chromosome 4. Using Hapmap SNP genotype frequency data for *FGF2* SNPs, we estimated that the 25 SNPs presented in this report capture 97% of the known common variation ($\text{MAF} \geq 0.05$) across the *FGF2* locus at $r^2 \geq 0.8$ for pairwise correlations. To the best of our knowledge, this is the first study to evaluate *FGF2* SNPs in a large multi-center study. Based on the method of Purcell et al. (Purcell et al., 2003) we estimated that we had $\geq 80\%$ power to detect ORs of 1.20 at an alpha of 0.05 for the 19 SNPs with $\text{MAFs} \geq 0.1$ (Table 2). However, we acknowledge that we had considerably less power to detect these effect sizes with the six SNPs with $\text{MAFs} < 0.1$.

Our study highlights the importance of consortium-based approaches to investigating putative genetic association in case-control analyses, particularly for low-risk genes that require large sample sizes to detect small SNP effects. We note that three SNPs, in addition to the rs308447, achieved the minimal level of significance of $p \leq .05$ in study-specific per-allele estimates (data not shown), but not in the combined analysis. If we had reported the results of these individual case-control studies, it may have led other groups to attempt replication but our combined analysis provides a more accurate assessment of these associations and reduces publication bias.

FGF2 has been the focus of a plethora of studies into human tumor biology and has important implications for cancer therapies and clinical outcomes. *FGF2* is one of several fibroblast growth factor molecules that interact with various vascular endothelial growth factors and cell surface receptors that are known to play a role in tumor growth and angiogenesis (Powers et al., 2000; Presta et al., 2005). The correlation between angiogenesis and the extent of metastatic disease has been widely demonstrated in a large and diverse range of human cancers (Macchiarini et al., 1992; Weidner et al., 1993; Weidner et al., 1991) including advanced stage ovarian carcinoma (Hollingsworth et al., 1995; Weidner, 1995). Abnormally high concentrations of

FGF2 have been found in the serum of patients with active metastatic cancers and have been shown to correlate significantly with extent of disease, clinical status and risk of future mortality (Nguyen et al., 1994). These findings would support the assessment of *FGF2* polymorphisms with regard to ovarian cancer survival and prognosis in future studies. To date several functional angiogenic gene SNPs have been studied in solid cancers with varying results derived from sample sizes that are too small to detect the modest effects anticipated from these low penetrance genes (Balasubramanian et al., 2002). Large-scale epidemiologic studies of other genes involved in angiogenesis are therefore warranted to further enhance our understanding of tumor progression. This could lead to novel approaches to risk stratification or the use of anti-angiogenic treatment strategies, if angiogenic potential, and hence prognosis, can be predicted according to individual genotype.

Acknowledgment

The AOCS Management Group (D. Bowtell, G. Chenevix-Trench, A. deFazio, D. Gertig, A. Green, P. Webb) gratefully acknowledges the contribution of all the clinical and scientific collaborators (see <http://www.aocstudy.org/>). The AOCS and ACS Management Group (A. Green, P. Parsons, N. Hayward, P. Webb, D. Whiteman) thank all of the project staff and collaborating institutions. We also thank all the participants in all the participating studies.

Grant support: National Health and Medical Research Council of Australia (199600, ACS study; GCT and PW), U.S. Army Medical Research and Materiel Command under DAMD17-01-1-0729, the Cancer Council Tasmania and Cancer Foundation of Western Australia (AOCS study); and NIH R01 CA122443, R01 CA112523 and R01 CA87538 (DOVE study; JAD and MAR); the Mayo Foundation (MAYO study; EG, DR, RV, SA). Some of this work was funded by the California Cancer Research Program grants 00-01389V-20170 and 2110200, U.S. Public Health Service grants CA14089, CA17054, CA61132, CA63464, N01-PC-67010 and R03-CA113148, and California Department of Health Services sub-contract 050-E8709 as part of its statewide cancer reporting program.

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