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A Prospective Study of Risk-Reducing Salpingo-oophorectomy and Longitudinal CA-125 Screening among Women at Increased Genetic Risk of Ovarian Cancer: Design and Baseline Characteristics: A Gynecologic Oncology Group Study

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Abstract

Background—Women who are genetically predisposed to ovarian cancer are at very high risk of developing this disease. Although risk-reducing salpingo-oophorectomy (RRSO) and various screening regimens are currently recommended to reduce ovarian cancer risk, the optimal management strategy has not been established nor have multiple additional issues been adequately addressed. We developed a collaboration among the Clinical Genetics Branch (National Cancer Institute's Intramural Research Program), the Gynecologic Oncology Group (GOG), and the Cancer Genetics Network to address these issues.

Methods—This is a prospective, international, two-cohort, nonrandomized study of women at genetic risk of ovarian cancer, who chose either to undergo RRSO or screening, at study enrollment. Primary study objectives include quantifying and comparing ovarian and breast cancer incidence in the two study groups, assessing feasibility and selected performance characteristics of a novel ovarian cancer screening strategy (the Risk of Ovarian Cancer Algorithm), evaluating various aspects of quality of life and nononcologic morbidity related to various interventions in at-risk women, and creating a biospecimen repository for subsequent translational research.

Results—Study accrual is complete as of November 2006; 2,605 participants enrolled: 1,030 (40%) into the surgical cohort and 1,575 (60%) into the screening cohort. Five years of prospective follow-up ends in November 2011. Verification of BRCA mutation carrier status is under way, either through patient-provided reports from clinical genetic testing done before

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enrollment or through research-based genetic testing being conducted as part of the protocol. Patient eligibility is currently under evaluation and baseline, surgical, pathology, and outcome data are still being collected. The study design and selected baseline characteristics of cohort members are summarized.

Conclusion—This National Cancer Institute intramural/extramural collaboration will provide invaluable prospectively collected observational data on women at high familial ovarian cancer risk, including substantial numbers of women carrying BRCA1/2 mutations. These data will aid in elucidating the effect of RRSO on breast/ovarian cancer risk and the effects of two management strategies, on quality of life and other issues that may influence patient care, as well as providing preliminary estimates of test specificity and positive predictive value of a novel ovarian cancer screening strategy.

Introduction

In this article, we present the rationale, design, and selected baseline characteristics for Gynecologic Oncologic Group Protocol 199 (GOG-199), A Prospective Study of Risk-Reducing Salpingo-oophorectomy (RRSO), and Longitudinal CA-125 Screening among Women at Increased Risk of Ovarian Cancer.

Ovarian cancer accounts for ~3% of all cancer cases diagnosed in the United States each year and is the leading cause of death from gynecologic malignancy (1). Five percent to 10% of all ovarian cancer cases are associated with mutations in high-penetrance susceptibility genes associated with the Hereditary Breast/Ovarian Cancer syndrome (HBOC), most notably *BRCA1* and *BRCA2* (2), or one of the mismatch repair genes (*MLH1, MSH2, MSH6,* and *PMS2*) responsible for hereditary nonpolyposis colorectal cancer (3, 4). Depending on the selection criteria used, the cumulative probability of developing ovarian cancer by age 70 years ranges from 16% to 40% in HBOC (2) and is ~12% in hereditary nonpolyposis colorectal cancer (5) compared with the general population lifetime risk of 1.5% in U.S. White women (6). Primary fallopian tube carcinoma is also a syndromic malignancy among *BRCA1/2* mutation carriers, with an estimated lifetime risk of 1.1% to 3.0% compared with 0.025% in the general population (7–9). Ovarian cancer risk is also increased in women who have a family history of ovarian cancer, that is, families in which no mutation has been identified in affected family members.

The discovery of these ovarian cancer susceptibility genes and the implementation of clinical mutation testing (10–13) aimed at identifying specific at-risk individuals have led to increasing numbers of high-risk women facing decisions regarding cancer risk management options. RRSO on completion of childbearing represents a potentially valuable intervention, as it has been shown to reduce ovarian cancer risk by 80% to 90% (14, 15) and breast cancer risk by 50% to 60% (15) in *BRCA* mutation carriers.

However, RRSO does not eliminate the risks of ovarian cancer completely, because women may still develop primary peritoneal carcinomatosis (16, 17), which is clinically and histologically indistinguishable from ovarian cancer. Moreover, RRSO is an irreversible intervention and has the potential for significant short-term morbidity, especially symptoms related to acute estrogen deprivation and sexual dysfunction (18), as well as inadequately evaluated long-term morbidity in premenopausal women. Surgical menopause is associated with significantly increased risks of cardiovascular disease and bone loss/fracture in the general population (19–21), and it is reasonable to anticipate similar morbidity in genetically at-risk healthy women. Thus, these risks need to be evaluated in the context of recent evidence suggesting that RRSO may be associated with significant improvements in both cancer-specific and overall mortality (22).

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Tubal ligation (without oophorectomy), another potential surgical intervention, is associated with ~50% reduction in ovarian cancer risk both in the general population (23–27) and among retrospectively studied *BRCA1* mutation carriers (28). Although not widely used, tubal ligation may represent a short-term risk-reducing strategy for selected young women who have completed childbearing but who prefer to delay RRSO until closer to natural menopause.

Administration of oral contraceptives represents a viable prevention option for high-risk women. Oral contraceptives are associated with a 50% reduction in sporadic ovarian cancer risk in the general population, which is both dose dependent and sustained after these medications are discontinued (29, 30). Although initial studies of oral contraceptives as a chemoprevention modality for hereditary ovarian cancer were contradictory (31, 32), more recent data have indicated a risk reduction of similar magnitude to that seen in the sporadic setting (33, 34). Potential drawbacks to the use of oral contraceptives as chemopreventive agents in this context include concerns regarding the usual side effects associated with these agents, particularly an increased risk of thrombotic events, and concerns that these hormonal agents may increase breast cancer risk in women from HBOC families. However, recent studies suggested that up to 5 years' use of oral contraceptives was not associated with further increase in breast cancer risk among mutation carriers (35, 36).

Ovarian cancer screening (OCS) has been suggested as an alternative to RRSO in genetically at-risk women, with the hope that early detection may increase the chance of cure. However, neither the efficacy of screening nor the optimal screening strategy for high-risk women is known. Furthermore, available data suggest that the most commonly employed screening regimen [twice yearly CA-125 plus concurrent transvaginal ultrasound (TVUS)] is not adequate in high-risk women (37). Since the inception of this study, additional data have confirmed that OCS with pelvic examination, CA-125 measurements, and TVUS in varying combinations fails to detect early ovarian cancer reliably in high-risk patients (38–40).

The Risk of Ovarian Cancer Algorithm (ROCA), a novel screening strategy that estimates the likelihood of having undetected ovarian cancer from a Bayesian evaluation of longitudinal CA-125 determinations followed by secondary screening with TVUS if indicated, appears to have better performance characteristics than the current approach of employing a standard CA-125 cutoff value when studied in women at general population risk (41–44). However, this strategy has not yet been systematically evaluated in women at increased genetic risk of ovarian cancer.

Advances in molecular genetics and increasing patient and healthcare providers' awareness have created a need for accurate clinical and pathology data to assist healthcare providers and high-risk patients in making management decisions. Once it became practical to identify specific subjects who were genetically predisposed to developing the manifestations of a particular syndrome, HBOC in this instance, a host of pressing clinical questions arose, among them the levels of risk and penetrance of the syndromic cancers; the natural history of these cancers compared with their sporadic counterparts; the indications, risks, and benefits of genetic testing; the possibility of genotype-phenotype correlation and gene-environment interactions; the risks, benefits, and limitations of disease-specific screening and risk-reducing interventions; and the effects of the knowledge of mutation carrier status on the decisions regarding various risk management strategies and quality of life. Information regarding risk management is also of great importance for women who are *BRCA1/2* mutation negative but are otherwise at high familial ovarian cancer risk, that is, women with a strong family history of breast and/or ovarian cancer but in whose family no known genetic mutation has been identified.

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When this protocol was being designed in 2000 to 2003, considerable progress had been made toward answering some of these questions. However, methodologic issues related to the design of most of these studies created uncertainty regarding the accuracy and precision of the estimates that had been published. These issues included retrospective study designs, study populations of limited sample size and/or follow-up, recruitment of highly selected participants from high-risk clinics located at tertiary referral centers or from special populations (e.g., subjects of Ashkenazi Jewish heritage, selected for the presence of three *BRCA* founder mutations), not studying *BRCA1* and *BRCA2* mutation carriers separately, incomplete breast and ovarian cancer risk factor data collection, and failure to account for the effect of prophylactic surgery on the subsequent risk of cancer. Moreover, most previous studies did not address the effect of management decisions on quality of life or on long-term nononcologic morbidity.

At the same time, formal cancer genetic risk assessment and clinical *BRCA* germ-line mutation testing were becoming a widely known and accepted clinical practice among healthcare providers and the general public. Thus, a large, well-designed, international prospective study was needed to address some of these important, but understudied, issues. Towards that end, investigators from National Cancer Institute's Clinical Genetics Branch, the Gynecologic Oncology Group (GOG), and the Cancer Genetics Network (CGN) collaborated to study prospectively a cohort of women at high familial risk of ovarian cancer, to test the feasibility of using ROCA, and to characterize certain performance characteristics of this novel OCS algorithm in the high-risk setting. The information to be gained from this collaboration will be invaluable for women with identified *BRCA1/2* mutations and other women at high familial risk, and for their healthcare providers, as they make decisions aimed at managing the risks related to familial ovarian cancer.

Materials and Methods

Study Design

GOG-199 is a multi-institution, prospective two-cohort, nonrandomized study of women at increased familial/genetic risk of ovarian cancer. A woman was eligible for study if she was at high genetic risk of ovarian cancer and met other eligibility criteria (Table 1). In brief, women were eligible if they or a close relative carried a deleterious *BRCA1/2* mutation or if they reported a family history of breast and/or ovarian cancer that was associated with >20% prior probability of being a mutation carrier. The study opened to patient accrual in July 2003.

Objectives

Cancer Prevalence and Incidence—We will estimate from prospectively collected data the incidence of ovarian cancer, fallopian tube cancer, breast cancer, primary peritoneal carcinomatosis, and all cancers among women at increased ovarian cancer risk enrolled in this study, with a special emphasis on known *BRCA1/2* mutation carriers. We also will analyze these incidence rates in women who are not *BRCA1/2* mutation carriers but who have a strong family history of breast and/or ovarian cancer. The strong family history scenario is more common clinically than is a mutation-positive family, but nearly all the data related to management are derived from the latter. Currently, these management strategies are assumed (but unproven) to be appropriate for mutation-negative/family history–positive women as well. Precise point estimates of these cancer rates will be developed separately for subjects in the RRSO and the OCS cohorts, and the reduction in breast and ovarian cancer incidence associated with RRSO will be estimated. By comparing cancer incidence rates between these two groups of women, our objective is to more precisely understand the impact of RRSO on syndromic cancer incidence.

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Incidental discovery of ovarian cancer and fallopian tube cancer at the time of RRSO has been reported (45). Thus, the prevalence of clinically occult ovarian cancer and fallopian tube cancer, as well as precursor lesions among women undergoing RRSO, will also be estimated in this study. This information could provide valuable insights into the natural history of familial ovarian cancer and into the potential for early intervention.

Evaluation of the ROCA—The second major study objective is to evaluate the feasibility and selected performance characteristics (including positive predictive value and specificity) of ROCA, a novel, intensive OCS regimen. Normal ranges and distributions of CA-125 will be established for the entire cohort, as well as by specific clinical characteristics, including *BRCA* mutation carrier status, menopausal status, hormone replacement therapy usage, and RRSO status. Furthermore, we plan to evaluate the effect of various factors that may modify CA-125 levels, which could potentially lead to modifications of the existing ROCA algorithm that would improve its performance.

BRCA1/2 Mutation Testing—Scientifically, we felt that it was essential to know the *BRCA1/2* mutation status of all study participants, because we had a particular interest in the subset of women who are *BRCA* mutation negative/family history positive, who represent the more common clinical scenario in cancer genetics practice. We anticipated that (*a*) many participants would have undergone clinical mutation testing before enrolling in the study and (*b*) many would have chosen not to learn their mutation status for a variety of reasons including concerns about genetic discrimination. Nonetheless, our experience with HBOC family members led us to believe that the latter group of women would understand and support the need for *researchers* to know their mutation status. Therefore, research-based mutation testing was done on previously untested participants, who were informed that these results “would not routinely be disclosed” to them. However, we also recognized that it was ethically and legally problematic to refuse to disclose this information to subjects who specifically requested it. We therefore built into the protocol and consent form a mechanism by which participants could request disclosure of their research-based BRCA mutation test results. This process mandated that such tests must be repeated in a Clinical Laboratory Improvement Amendments–certified laboratory, and confirmed at the participant’s own expense, before results could be disclosed to the patient and used for clinical decision-making. This latter activity would take place outside the formal structure of the protocol, using standard genetic risk assessment and counseling resources and procedures, to ensure that these women fully understood the risks and benefits of learning their mutation status.

Evaluation of Potential Biomarkers of Ovarian Cancer and Breast Cancer Risk —A large and systematic collection of serially acquired biological materials will be an invaluable resource in future evaluations of potential bio-markers of ovarian and breast cancer risks. We have established a biospecimen repository of DNA, benign and malignant tissue from RRSO, and serial serum/plasma samples for future translational studies aimed at identifying biomarkers of ovarian and breast cancer risk, genetic modifiers of familial cancer risk, and disease mechanisms.

Quality of Life—To understand better the effect of choosing RRSO versus OCS on quality of life among high-risk women, we are collecting data using validated psychometric instruments (that is, Medical Outcome Study Short Form-36, Impact of Events Scale, Center for Epidemiological Studies Depression Scale, Speilberger State-Trait Anxiety Scale, Sexual Activity Questionnaire, Multidimensional Impact of Cancer Risk Assessment, Endocrine Subscale of the FACT, and Lerman Cancer Worry Scale) at baseline and periodically during prospective 5-year follow-up.

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Medical-Decision Making—The choice between RRSO and OCS is likely influenced by many factors. We are assessing the potential effect of sociodemographic, psychosocial, and health-related factors, among others, on this decision-making process, both for the initial decision at enrollment and for screening arm participants who elect to crossover to surgery.

Nononcologic Sequelae of Premature (Surgical) Menopause—The long-term morbidity of premature menopause in high-risk women is not well established. We are evaluating the incidence of conditions that may result from long-term estrogen deficiency, such as osteoporosis, skeletal fractures, coronary artery disease, and myocardial infarction. We are monitoring the use of medications related to important study outcomes (e.g., exogenous hormones, bisphosphonates, and cardiovascular agents). Furthermore, in an effort to mitigate the adverse consequences of RRSO in premenopausal women, we incorporated into the protocol recommendations for managing menopause-related morbidity and are monitoring adherence to health maintenance recommendations.

Although we do not expect the immediate surgical complications associated with RRSO to be different from those seen with oophorectomy for other reasons, we are monitoring the adverse events related to surgery among women undergoing RRSO.

Breast Cancer Risk Reduction—RRSO has been shown to reduce breast cancer risk among *BRCA* mutation carriers. Women at high ovarian cancer risk who are members of HBOC families are also at increased breast cancer risk. Quantifying the magnitude of breast cancer risk reduction among women who have undergone RRSO is another study objective.

The extensive list of study goals as detailed above was justified by recognizing that this complex, comprehensive and costly study would not soon be replicated; thus, it was essential that the current cohort be used to achieve maximum scientific and clinical benefit.

Recruitment Campaign—GOG-199 represented a novel study design for the GOG, a cooperative group best known for its clinical trials of new treatment strategies for various gynecologic malignancies. Unlike the usual setting, in which patients with established cancer have an incentive to participate in treatment trials targeting life-threatening disease, GOG-199 recruited healthy women with strong histories of breast and ovarian cancer. The potential utility of RRSO was not widely known in the general community, and many healthcare providers were reluctant to remove “healthy organs” in an effort to reduce cancer risk. We judged that a special effort was required to meet this protocol’s accrual goal. A comprehensive recruitment campaign was implemented, which included:

- A study-specific Web site with an interactive patient self-referral tool (http://ovariancancer.gog199.cancer.gov). This site has averaged ~900 visitor sessions a month since the study opened (Fig. 1);
- A study-specific patient recruitment brochure, which was distributed widely through physician’s offices, patient advocacy groups, and the study Web site (http://ovariancancer.gog199.cancer.gov/Brochure_021204.pdf);
- A pocket-sized study eligibility criteria reference card for participating healthcare providers;
- Direct mailing of recruiting letters/brochures to American Society of Clinical Oncology, American Society of Obstetrics and Gynecology, Society of Gynecologic Oncologists, American College of Medical Genetics, National Society of Genetic Counselors, and Oncology Nursing Society members;

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- E-mail outreach to >700 National Cancer Institute–related patient advocacy organizations, plus personal telephone contact with the 40 organizations specifically interested in ovarian cancer research, requesting that (*a*) a link to the GOG-199 study site be placed on their organization's Web site home-page, (*b*) the study brochure be distributed at national meetings, and (*c*) articles regarding the study appear in their periodic newsletters;
- Development of a PowerPoint presentation for GOG-199 investigators to facilitate their describing the protocol during teaching, professional, and lay outreach activities;
- Brief "drop-in" story templates describing the study, provided to participating institutions, to obtain local newspaper coverage for their role in GOG-199;
- Various educational materials for patients and healthcare providers with general management guidelines for nononcologic complications of premature menopause (http://ovariancancer.gog199.cancer.gov/PrematureMenopause_082404.pdf) and detailed management information for symptoms related to estrogen deficiency (http://www.ovariancancer.gog199.cancer.gov/SurgicalMenopause_120806.pdf);
- Public service announcements through the NIH Network of Radio Stations, which broadcasts health/science stories to the general public; and
- National stories in various media during Ovarian Cancer Awareness month.

It is difficult to discern which, if any, were central to the accrual success of the study. Judging by the number of visits to the study Web site in general and the self-referral tool in particular, it would appear that this was an important component of the recruitment plan.

Management Choices—Eligible patients selected either RRSO or OCS as their management option, in conjunction with advice offered by their various healthcare providers. OCS consisted of applying ROCA to classify participants as being at low, intermediate, or elevated likelihood of having ovarian cancer. Subsequent evaluation for ovarian cancer was guided by the ROCA results (Fig. 2). OCS subjects underwent annual TVUS. The OCS cohort of GOG-199 was, with several specific exceptions, virtually identical to the CGN ROCA Screening Trial, which opened to patient accrual in 2001. The major differences between the two screening protocols were that, unlike the CGN version, GOG-199: (*a*) did not permit enrollment of women who had undergone RRSO before study enrollment, (*b*) required a baseline TVUS before study enrollment, (*c*) collected DNA from all study participants, (*d*) collected copies of clinically based *BRCA* mutation test results from women who had been tested, (*e*) planned research-based *BRCA* mutation testing for all participants who had not been tested clinically, and (*f*) included a study-specific data collection instrument focused on medical decision-making and quality of life. The two protocols were explicitly harmonized to permit exchange of data between GOG-199 (OCS cohort) and CGN for pooled analyses aimed at evaluating and refining the ROCA algorithm.

Study participants who enrolled in the OCS cohort were permitted to crossover to RRSO at a later date, either electively (because a participant changed her mind regarding the preferred approach to risk reduction) or diagnostically, (as a consequence of evaluating elevated ROCA scores, abnormal TVUS findings, or clinical symptoms), with no malignancy found at surgery. Subsequent to crossover, participants were followed in the same manner as women who initially elected RRSO. Participants diagnosed with a malignancy requiring chemotherapy or radiation therapy during follow-up were taken off-study and followed annually (Fig. 2).

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Protocol-based RRSO consisted of visual inspection of the peritoneal cavity, removal of both ovaries and fallopian tubes with meticulous processing of the surgical specimen, including 2-mm serial sections through both the ovaries and the fallopian tubes, and peritoneal lavage cytology. Hysterectomy was not required per protocol but could be electively done as medically indicated. Aliquots of normal ovary and fallopian tube, peritoneal lavage supernatant, and tumor tissue (if present) were cryopreserved. ROCA determination was done at baseline and every 6 months for participants in the RRSO cohort (Fig. 2).

Data Collection—The schedule of protocol-required biospecimen and data collections for both cohorts is summarized in Table 2. For all participants, DNA was obtained at baseline for research-based *BRCA1/2* mutation testing of those whose mutation status was unknown. Serum and plasma were collected either quarterly (OCS cohort) or twice yearly (RRSO cohort) for ROCA determination. A biospecimen repository of DNA, serum, and plasma was created from the materials collected. All participants were to complete a TVUS, a baseline family and personal history questionnaire, a baseline quality of life questionnaire, and a medical decision-making questionnaire at both enrollment and at the time of crossover from OCS to RRSO. All RRSO-related surgical material was handled in a standardized fashion and subjected to central pathology review, data abstraction, and digital imaging of "lesions of interest." Benign and malignant tissues from RRSO were also collected for the repository. Additional specimen and data collection during follow-up is detailed in Table 2. Because participants in this study are at increased risk of both ovarian cancer and breast cancer, regular mammography was recommended as part of the routine, ongoing medical care for women with at least one intact breast and was expected to be done at least once a year by their health providers. Selected study forms and data collection instruments are available online at http://dceg.cancer.gov/QMOD/qmod_titles.html.

Sample Size and Power Calculations—Assessment of statistical power focused on the primary comparison of incidence rates of ovarian and breast cancer among carriers of *BRCA1* or *BRCA2* mutations. These patients were expected to be significantly more likely to develop these cancers than noncarriers, and by powering the study on this subset of subjects, adequate numbers would be assured for comparison of incidence rates of all participants. Age-specific estimates of the 5-year risk of developing ovarian and breast cancer in carriers of *BRCA1* and *BRCA2* mutations were based on prediction models developed by Parmigiani et al. (46), and the assumed age distribution of GOG-199 participants was based on the age distribution of a cohort of women having RRSO previously at Memorial Sloan Kettering Hospital. These estimates led to average estimated 5-year risks of ovarian and breast cancer of 0.043 and 0.138, respectively, for mutation carriers. Assuming a 1:1 ratio of screening to RRSO subjects, ~800 *BRCA1/2* mutation carriers would be required to have 90% power for detecting a ≤90% reduction in 5-year ovarian cancer risk due to RRSO, with a two-sided type I error rate limited to 0.05. This number of mutation carriers would also provide 90% power to detect a 50% reduction in 5-year breast cancer risk due to RRSO. We estimated that 1,800 subjects were required; they were expected to consist of 1,000 RRSO subjects and 800 screening subjects. With 1,000 RRSO subjects, estimates of the prevalence of clinically occult ovarian cancer at the time of surgery would have precision (95% confidence interval limits about the estimated prevalence) of ±0.01, assuming the true prevalence is ~0.03, and precision of ±0.02 assuming the true prevalence is ~0.12. With 800 screening subjects, the specificity of ROCA as well as the positive predictive value of ROCA could be estimated with precision of ±0.03 or less. Two years into the study, the accrual targets were reevaluated based on observed data from the first 1,544 subjects, and the sample size was increased 2,332 patients to ensure a total of 800 mutation carriers. This report summarizes

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selected baseline characteristics of the two cohorts. Age distributions are characterized by medians and interquartile ranges. Interquartile range is defined as the 25th to 75th percentile.

Results

Study Accrual

The study began recruitment on June 16, 2003 and closed to new patients on November 3, 2006, after accruing 2605 participants: 1,030 women in the RRSO cohort and 1,575 women in the OCS cohort. The accrual goal of 2,332 was surpassed by 273 subjects. A total of 158 GOG sites activated the study, including sites throughout the United States and Australia (Fig. 1). Accrual ranged from 1 to 148 subjects per site. Seven major institutions accounted for 25% of patient accrual, with 120 additional centers contributing one or more patients to the study. Initially, accrual to the screening cohort was much higher than to the RRSO cohort (Fig. 3). By mid-2005, screening cohort accrual was rapidly approaching the planned goal of 800, which led to consideration of closing the screening cohort to new accruals while continuing RRSO enrollment. In anticipation of potential screening cohort closure, there was a marked surge in screening accruals. The decision to continue accrual to both cohorts was followed by a sharp drop in enrollment to the screening cohort, whereas RRSO enrollment rose steadily through the end of the study.

Baseline Characteristics

Selected baseline characteristics of the cohort are shown in Table 3. Sixty percent enrolled in OCS versus 40% choose RRSO. Ninety-four percent of study participants were White, 3% were Black, and 2% were Hispanic. Nineteen percent were of Ashkenazi Jewish heritage. Women from the screening cohort were slightly younger than those in the RRSO cohort (median age, 47.2 versus 48.1 years) and correspondingly more likely to be premenopausal (63% versus 58%) than were women in the RRSO cohort. More patients in the RRSO cohort reported carrying a *BRCA1/2* mutation than in the OCS cohort (48% versus 18%). Similar proportions of RRSO and OCS participants reported a positive family history of breast cancer (78% for both) and ovarian cancer (48% versus 49%), respectively. A larger proportion of the RRSO cohort reported a personal history of breast cancer before enrollment than did the OCS cohort (51% versus 37%).

Protocol Evolution

Several major adjustments to the original protocol have occurred during its conduct. The first was the change in accrual goals, as described previously, to ensure that the number of mutation carriers required by the statistical design was reached.

The second set of major changes resulted in a substantial decrease in the data collection burden for both participants and research staff. This was required in response to the very large data management task that had been created by the initial study design, which was subsequently exacerbated by the increased accrual goals. We were compelled to decrease the demands on patient time to sustain acceptable protocol compliance rates and to decrease the length and frequency of questionnaire administration to control escalating data processing costs. These goals were accomplished by decreasing the frequency of ROCA testing in the RRSO cohort from every 3 months to every 6 months as supported by preliminary data from the CGN screening study suggesting no obvious value to applying ROCA to women who were post-RRSO,14 eliminating the baseline and follow-up quality of life questionnaires for all women enrolled after April 24, 2006, reducing the frequency of the quality of life follow-

[14]Steven Skates (CGN), personal communication.

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up questionnaires for those who had enrolled before that date, and decreasing the frequency and length of the detailed medical follow-up questionnaire. We estimate that these steps reduced the volume of data collection activities by ~50%, without compromising the main study endpoints.

Discussion

GOG-199 is the first large prospective cohort study of individuals genetically predisposed to ovarian cancer to bring a broad epidemiologically based, multidisciplinary design to this biologically and socially complex disorder. The major strengths of GOG-199 include large sample size and 5-year prospective follow-up, better representation of the overall high-risk population than that usually seen in a tertiary referral setting, and definitive classification of all study participants with regard to *BRCA* mutation status. These will permit development of more accurate estimates of cancer risk and risk reduction than has previously been possible. The high proportion of enrollees reporting a positive family history of breast and ovarian cancer as well as a personal history of breast cancer suggest that we achieved our goal of enrolling women at high risk of ovarian cancer. Other study strengths are inclusion of both mutation-negative/family history–positive women and *BRCA* mutation carriers; a standardized RRSO surgical pathology specimen processing protocol; a novel OCS strategy that has never been evaluated in high-risk women; the collection/archiving of both normal and malignant ovarian and fallopian tube tissue from women undergoing RRSO; the collection and archiving of DNA plus prospective serial serum and plasma samples for subsequent genetic, biomarker, and etiologic translational research; comprehensive assessment (both at baseline and during follow-up) of quality of life, including sexual functioning and cancer worry issues, among women electing two very different strategies aimed at managing their ovarian cancer risk; systematic evaluation of the factors that influence the choice between surgery and screening, both at study entry and at the time of crossover from RRSO to OCS; and obtaining pilot data on the utilization over time of diagnostic procedures and medications related to the nononcologic conditions associated with surgical menopause.

Weaknesses of this study include nonrandomized design (unavoidable), potential for inconsistencies in data collection procedures given the large number of contributing institutions, and potentially significant incomplete data and dropout rates. To date, we have no indication that either of the latter two issues is affecting this study, but a formal assessment has not yet been done. Additionally, it will take a long time to collect the necessary data and do primary study analyses on these data, a direct and unavoidable consequence of its prospective design.

Protocol GOG-199 appears to be well on its way towards meeting its planned goals. A model that describes factors correlated with the decision to undergo RRSO will soon be submitted for publication. Based on material from GOG-199, investigators are developing a protocol (GOG CPC-610) to contribute annotated DNA samples and genotype data from GOG-199 participants who are mutation carriers to the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* for studies of genetic variations that influence *BRCA*-associated cancer risks (47). This effort can improve estimates of cancer risk by characterizing risk from particular variants of *BRCA1* and *BRCA2* and by identifying genetic and other modifiers of risk from BRCA mutations. Such studies may give insight into the etiology of *BRCA*-related cancers.

The resources from this study have formed the basis for development of subsequent projects whose objectives complement those of GOG-199. Examples include (*a*) short-term, presurgical chemoprevention pilot trials with fenretinide (GOG-190) and lovonorgestrel

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(GOG-214); (*b*) post-RRSO phase II trial of zoledronic acid for maintaining bone health in women with surgical menopausal (GOG-215); and (*c*) a comprehensive assessment of the joint effects of mammographic density, *BRCA* mutation status, and RRSO on the prospective risk of developing breast cancer (GOG CPC-412).

During the course of study development and patient accrual, several valuable lessons were learned. First, a large study of this size can only be accomplished through the collaboration of many institutions and investigators. Various investigators bring different perspectives that need to be integrated to shape the protocol and research process. The wide-ranging interests of investigators create pressure to study many questions and require extensive data collection. In fact, the amount of data we attempted to collect became overwhelming for study staff and a burden for patients and had the potential to decrease participation and compliance. It was therefore necessary to reduce the data collection, without jeopardizing main study objectives. Ideally, data requirements would have been trimmed to a necessary minimum before the study was launched.

Several specialized, protocol-specific tools were developed and distributed to support the research staff at active study sites, including a brief procedures manual summarizing step-by-step exactly what needed to be done at each follow-up point, and a simple but systematic spreadsheet-based tracking program. Several protocol-related workshops were held at the GOG semiannual meetings to provide research staff opportunities to ask questions, make suggestions, and learn how to handle specific issues. An E-mail listserv comprised all study principal investigators and data managers from sites that had activated the protocol was implemented and used to communicate time-sensitive matters to study staff.

We also learned first-hand how changes in accrual plans can inadvertently affect recruitment. Although midcourse adjustments in accrual goals are not uncommon, the ambiguity created by our interim assessment of accrual resulted in a frantic surge of screening enrollment (in anticipation of possible closure of the screening arm) followed by a dramatic decline in screening enrollment once it was clear that the screening arm of the study would remain open (Fig. 3). The resulting fluctuations in accrual to each arm of the study might have been avoided had we been more circumspect in discussing our interim assessment plans.

Accrual to this study is now complete, and all patients are currently undergoing the planned 5-year follow-up, due to end in November 2011, at which time we will begin the analysis of primary study endpoints. In the meanwhile, the study staff will focus on collecting and maintaining the large amounts of data that are accumulating, tracking follow-up, and promoting compliance. This study promises to make a major contribution to improving the lives of women at increased genetic risk of ovarian cancer and advancing our understanding of the molecular pathogenesis of hereditary and familial ovarian and breast cancer.

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The success of this study to date represents the combined efforts of countless study managers, research nurses, investigators, statistical and data center staff, and scientific collaborators from individual GOG and CGN sites, GOG and CGN headquarters, intramural National Cancer Institute (Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics; Laboratory of Population Genetics, Center for Cancer Research), and extramural National Cancer Institute programs (Community Clinical Oncology Program, Division of Cancer Prevention; Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis; Clinical and Genetic Epidemiology Research Branch, Division of Cancer Control and Population Sciences), too numerous to mention by name. Their dedication and contributions to GOG-199 have been, and continue to be, essential, and to them all we

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express our deepest appreciation. Finally, we acknowledge with admiration and gratitude the most important contributors to this effort, the 2,605 women who have selflessly joined the study and given unstintingly of their time, energy, and tissue to advance our knowledge of familial/hereditary ovarian cancer.

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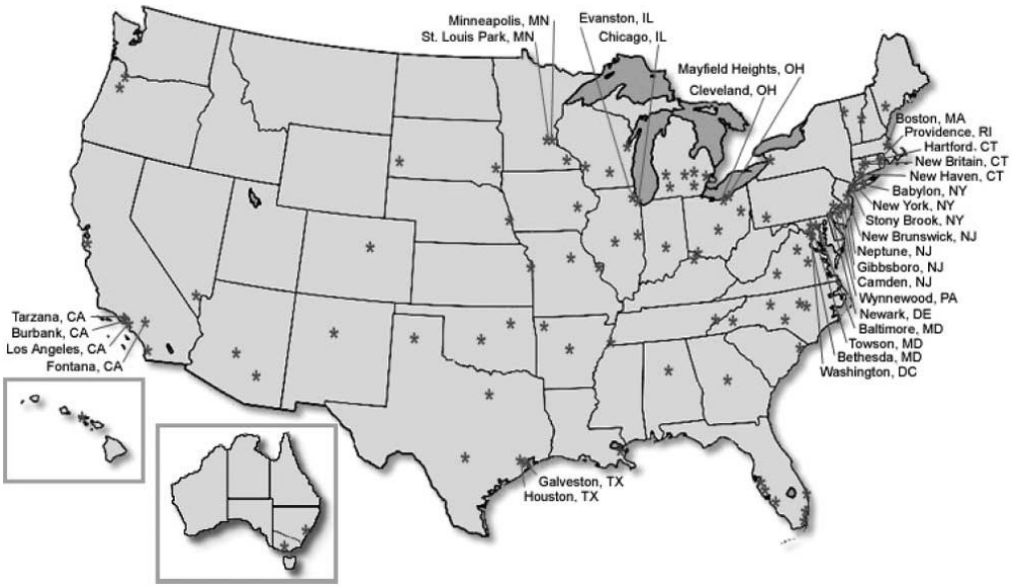

Figure 1.
Geographical distribution of GOG study sites at which GOG-199 was open to enrollment.

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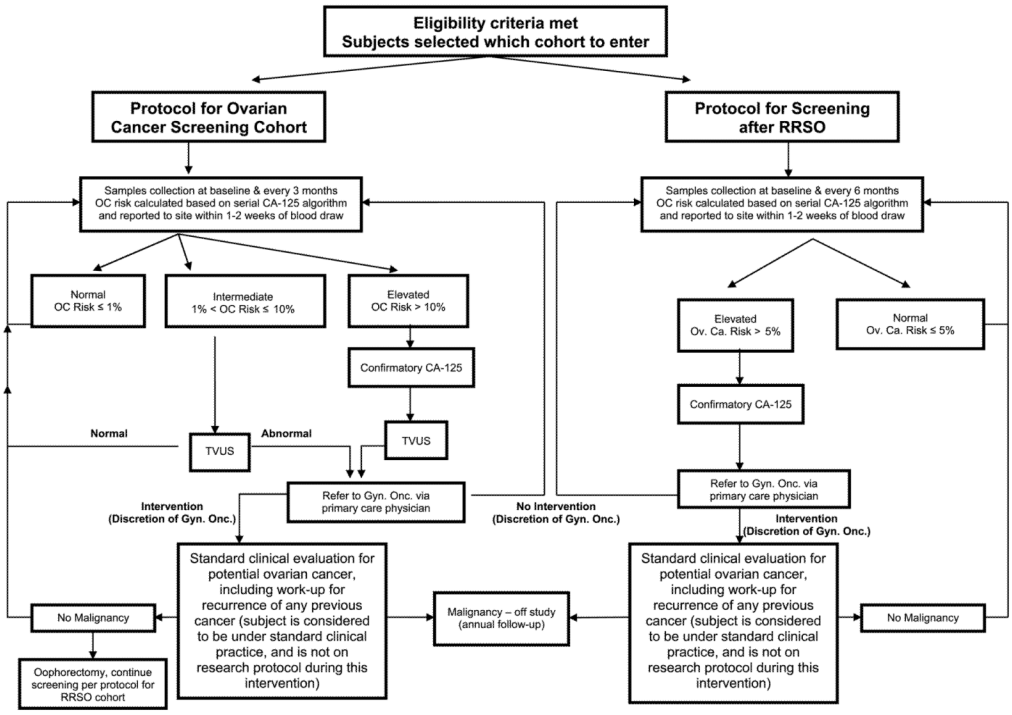

Figure 2.
GOG-199 study schema.

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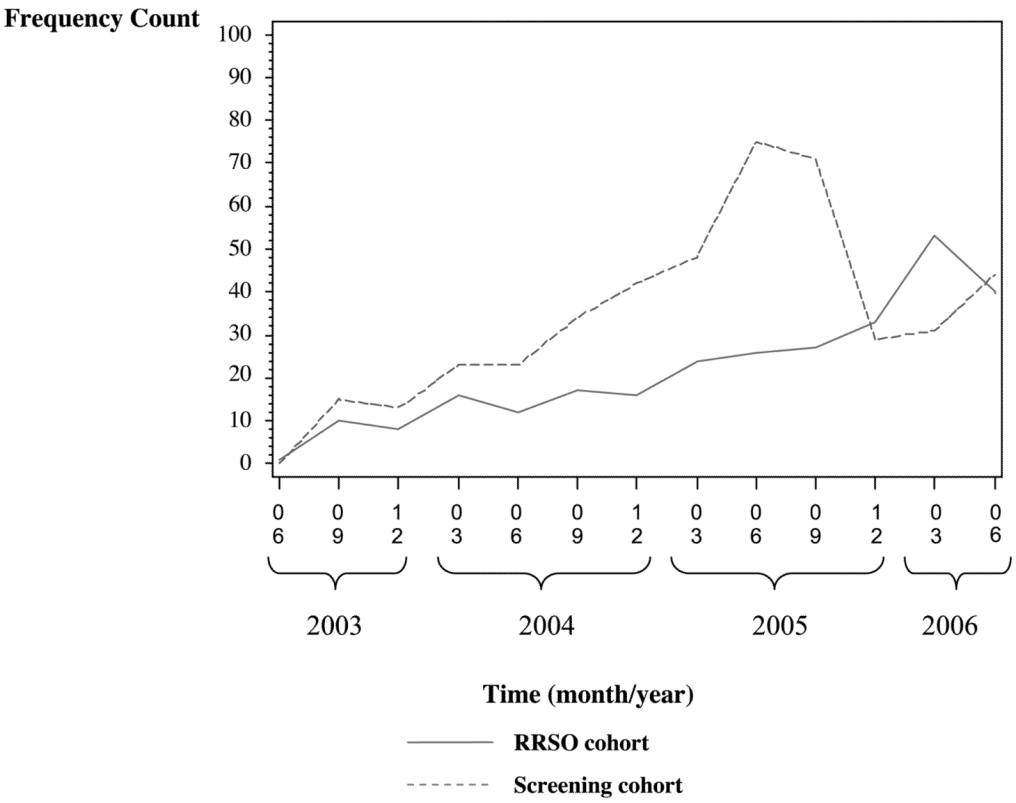

Figure 3.
Accrual to the surgical (RRSO) and screening cohorts of GOG-199 by month.

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Table 1

Eligibility and exclusion criteria for GOG-199

High genetic ovarian cancer risk criteria:	
1	A documented deleterious *BRCA1* or *BRCA2* mutation in either the subject herself or her first- or second-degree relative; or
2	Family history of at least two ovarian and/or breast cancers among the subject or first- or second-degree relatives of the subject within the same lineage;* or
3	The subject is of Ashkenazi Jewish ancestry and (*a*) has had breast cancer herself* or (*b*) has one first-degree or two second-degree relatives with breast and/or ovarian cancer;* or
4	The probability of carrying a *BRCA1/2* mutation given the family history of breast and ovarian cancers exceeds 20%, as calculated by BRCAPRO.†
Other eligibility criteria:	
1	Age of ≥30 y;
2	No prior history of ovarian cancer (including low malignant potential cancers or primary papillary serous carcinoma of the peritoneum); and
3	Having at least one intact ovary.
Exclusion criteria:	
1	Women who have a first- or second-degree relative with a deleterious *BRCA1/2* mutation and who have tested negative for the exact same mutation.
2	Women who are currently pregnant or planning pregnancy during the study.
3	Women who are participating in another ovarian cancer early detection trial (except for the ROCA study being run by the CGN).
4	Women with psychiatric, psychologic, or other conditions that prevent fully informed consent.
5	Women with current untreated malignancy, except nonmelanoma skin cancer.
6	Women with adjuvant radiation therapy or chemotherapy within the past 1 mo (31 d).
7	Women who have been treated for prior metastatic malignant disease within the past 5 y.
8	Women who have undergone i.p. surgery within the prior 3 mo (includes laparoscopy).
9	Women with a history of any medical condition, which places the subject at risk related to the need for donating blood for research purposes (e.g., chronic infectious diseases, severe anemia, or hemophilia).

* If breast cancer is required to fulfill this criterion, at least one breast cancer must have been diagnosed before menopause (or age at diagnosis ≤50 y if age at menopause is unknown).

† Euhus DM, Smith KC, Robinson L, et al. Pretest prediction of *BRCA1* or *BRCA2* mutation by risk counselors and the computer model BRCAPRO. J Natl Cancer Inst. 2002;94(11):844–51.

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Table 2

Schedule of study-related evaluations

Variable	Before enrolling	Baseline	Every 3 mo	Every 6 mo	Baseline, 6, 12, 24, and 60 mo	6, 12, 24, 36, 48, 60 mo	Annual	As needed
Cancer genetic risk assessment	X*							
Eligibility assessment	X							
Choice of treatment	X							
History and physical examination†		X						
Baseline Questionnaire		X						
Quality of Life Instruments‡					X			
Medical Decision-Making form		X						X§
Health Outcome Follow-up form						X		
Cancer Incidence form				X				X
Cancer Follow-up form								X‖
Pathology report		X RRSO						X¶
CA-125 for ROCA		X	X Screening	X RRSO				
TVUS		X**					X	X††
Mammogram (recommended)							X	
Whole blood (for DNA)		X						
Serum, plasma		X	X Screening	X RRSO				

*BRCAPRO calculation if necessary.

†May have been done up to 6 wk (42 d) before the date of study enrollment. Pelvic examination was not required.

‡Only patients enrolled before April 26, 2006 and include the following instruments: Medical Outcome Study Short Form-36, Impact of Events Scale, Center for Epidemiological Studies Depression Scale, Speilberger State-Trait Anxiety Scale, Sexual Activity Questionnaire, Multidimensional Impact of Cancer Risk Assessment, and Endocrine Subscale of the FACT.

§Medical Decision-Making form will also be completed when participants enrolled in the screening cohort of the study choose to undergo RRSO.

‖The Cancer Follow-up form is to be completed only for patients who are diagnosed with cancer and complete a Q0-0199 (Treatment Completion form).

¶For participants who undergo RRSO after having enrolled in the screening cohort of the study and for women who develop primary peritoneal carcinomatosis after having undergone RRSO.

**May have been done up to 3 mo (90 d) before the date of study enrollment as long as a report could be obtained.

††As dictated by ROCA.

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Table 3

Selected patient characteristics at baseline, by study cohort

Characteristics	Cohort, *n* (%)	
	RRSO (*n* = 1,030)	**Screening (*n* = 1,575)**
Age		
≤39	198 (19)	444 (28)
40–49	433 (42)	534 (34)
50–59	297 (29)	431 (27)
60–69	86 (8)	139 (9)
>70	16 (2)	27 (2)
Menopausal status		
Premenopausal	597 (58)	990 (63)
Menopausal	433 (42)	585 (37)
Race		
Asian	10 (1)	16 (1)
Black	37 (4)	39 (2)
Hispanic	19 (2)	25 (2)
White	960 (93)	1,478 (94)
Other/unspecified	4 (<1)	17 (1)
Ethnicity		
Hispanic	19 (2)	25 (2)
Non-Hispanic	928 (90)	1,487 (94)
Other/unspecified	83 (8)	63 (4)
Ashkenazi parent[1]		
No	758 (74)	1,119 (71)
Yes	169 (16)	320 (20)
Unknown/unspecified	103 (10)	136 (9)
Reported mutation status[1]		
Carrier of a *BRCA1/2* mutation	492 (48)	277 (18)
Noncarrier	102 (10)	327 (21)
Unknown/never tested/unspecified	436 (42)	971 (62)
Personal history of breast cancer[1]		
No	444 (43)	921 (58)
Yes	530 (51)	581 (37)
Unknown/unspecified	56 (5)	73 (5)
Family history of breast cancer[1]		
No	209 (20)	319 (20)
Yes	806 (78)	1,231 (78)
Unknown/unspecified	15 (1)	25 (2)
Family history of ovarian cancer[1]		
No	517 (50)	773 (49)

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Characteristics	Cohort, *n* (%)	
	RRSO (*n* = 1,030)	**Screening (*n* = 1,575)**
Yes	498 (48)	777 (49)
Unknown/unspecified	15 (1)	25 (2)