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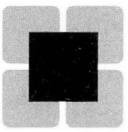

MAURIE MARKMAN, MD, EDITOR

The familial ovarian cancer registry: progress report

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BACKGROUND Ovarian cancer can be cured if detected early enough, but usually has already metastasized when diagnosed. A family history of ovarian cancer is still the strongest known risk factor.

OBJECTIVE To identify women at risk for ovarian cancer and design a program of surveillance.

METHODS Prospective registry of women with a family history of ovarian cancer.

RESULT From April 1991 to July 1993, 137 women (119 families), mean age 43, registered with the Familial Ovarian Cancer Registry. The 119 pedigrees revealed 171 cases of ovarian cancer. Only one family is undocumented by pathology. Forty of 137 registrants have more than one relative with ovarian cancer. Six percent of pelvic examinations were abnormal for potential adnexal disease. In 4% of registrants, initial CA125 concentrations were abnormal. Ultrasound examinations were abnormal in ovarian size (5%), in morphology (3%), and by resistive indices (4%). Four ultrasounds were repeated earlier than routine. Using "standard" fees, the total cost to diagnose the one case of ovarian cancer discovered was $68 848.

CONCLUSIONS This approach still cannot be considered cost-effective. We are continuing to search for genetic and molecular markers of disease in women at greatest risk and in their affected relatives.

INDEX TERMS: OVARIAN NEOPLASMS; REGISTRIES; COSTS AND COST ANALYSIS
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OF THE GYNECOLOGIC malignant diseases, ovarian cancer is the most common cause of death, accounting for 4% of all new cancers in women and 5% of all cancer-related deaths. This year, approximately 22 000 new cases will be diagnosed, and over 13 300 women will die of ovarian cancer.[1] Women living in industrialized countries have an estimated lifetime risk of acquiring ovarian cancer of 1 in 70.[2]

A variety of genetic, environmental, hormonal, and viral risk factors have been identified. However, only the familial risk appears secure in terms of etiology, and in this subpopulation the lifetime risk may approach one in two.[3] Three hereditary syndromes are currently identified: the site-specific ovarian syndrome, the breast-ovarian syndrome, and the Lynch syndrome II (ovarian, endometrial, and nonpolyposis-related colon cancer). These familial syndromes may account for up to 10% of cases of ovarian cancer.[4]

The problem is quite clear. Early-stage disease carries an excellent prognosis, with an apparent cure rate of over 90%.[5] How-

ever, in most series, once the tumor had metastasized, the 5-year survival rate rarely exceeded 25%.[6] Unfortunately, awaiting the arrival of symptoms or relying on routine physical examinations, 80% of patients presenting with ovarian cancer already have metastases at diagnosis.[7] Therefore, while we work to develop new forms of therapy for advanced disease, research efforts must also be directed towards diagnosing ovarian cancer early and understanding the molecular changes associated with its development and progression.

A variety of techniques have been employed to aid in the early diagnosis of ovarian cancer. Physical examination, as noted above, has resulted in the current stage distribution and is, therefore, inadequate alone. Measuring the serum concentration of the monoclonal antibody CA125 has been studied,[8] as has abdominal and vaginal ultrasonography, both with and without color Doppler.[9–11]

Combining the currently available tests yields a specificity exceeding 99%, but such an approach would not be cost-effective for screening in the general population: the prevalence of ovarian cancer is low (30 to 50 per 100 000), and the results would therefore have a low positive predictive value. In addition, definitive diagnosis requires laparoscopy or laparotomy.[12] It is hoped that familial registries will identify women at high risk, and that the current explosion in molecular investigation, newly discovered monoclonal antibodies, and radiological studies will allow more cost-effective early diagnosis in this high-risk population.

In 1981, the Familial Ovarian Cancer Registry (FOCR) was established at Roswell Park Memorial Institute in Buffalo, New York, to study the genetic transmission of this disease.[13] This, combined with the long-established efforts of Lynch and colleagues,[14] have provided others with the background for current investigations.

In April 1991, the FOCR was established at The Cleveland Clinic Foundation. We had three main goals: (1) to identify women who, based on family history, were at increased risk for developing ovarian cancer and to design a program of surveillance that addressed their specific risk and needs; (2) to develop a research data base to inform the women in our registry of new tests and other developments; and (3) to investigate the molecular changes involved in the promotion and progression of ovarian carcinoma and their possible use as diagnostic tests. This report reviews the first 2 years of this program.

MATERIALS AND METHODS

We mailed a description of the FOCR to several thousand physicians within our referral area to make them aware of the program. In addition, patient awareness was generated through an advertisement in a local newspaper.

As registrants were recruited, a relational database was created using the Paradox software program, version 3.5 (Borland International, Scotts Valley, Calif).

In our ongoing registry, women who call for an appointment or express an interest first receive a packet containing information about the registry (including costs and telephone numbers) and a personal demographic profile and genealogical chart to complete and return to us. The packet also contains authorization forms for release of medical information, specifically, microscopic slides, operative reports, and other pertinent information from relatives with cancer. Receiving and reviewing these data before the initial visit allows us to confirm the presence of ovarian cancer in the registrant's family and saves time.

During the initial visit, the patient undergoes a physical and pelvic examination. Blood is drawn for CA125 testing, and serum and white blood cells are banked. Vaginal ultrasonography with color flow Doppler is also performed on this day. The patient receives a letter 2 to 3 weeks after the visit summarizing the findings and giving her an initial estimate of her risk and recommendations for follow-up.

Follow-up recommendations are based primarily on careful examination of the registrant's pedigree, on the CA125 concentration (normal is considered ≤ 35 U/mL), and on the ovarian volume (normal in premenopausal women is considered ≤ 18 cm^3; in postmenopausal women, ≤ 8 cm^3; determined ultrasonographically using the prolate ellipsoid formula: anterior-posterior dimension × sagittal dimension × transverse dimension × .523). If an abnormality is found on ultrasonography or CA125 testing or both, depending on the patient's age, the test or tests are repeated within 1 to 3 months unless an obvious tumor has been characterized.

The screening ultrasonographic protocol involves obtaining: (1) measurements of the anterior-posterior, sagittal, and transverse dimensions of both ovaries; (2) images and measurements of any cystic or solid masses present; (3) a color image without Doppler tracing of the adnexa; (4) Doppler

tracings of the ovarian artery and vein outside and inside the ovary and of any mass (the arterial tracing also includes a resistive index with angle correction); (5) one sagittal or coronal image of the endometrium; and (6) measurements of the three largest "normal physiologic-appearing" cysts, if any are present.

The risk assessment is primarily determined by the pedigree and is frequently a group decision. It is based on the number and age of family members who have ovarian cancer; the presence or absence of related cancers of the breast, colon, endometrium, or prostate; and the histologic findings in the indexed case.

At first, we included only women older than age 25 who had at least one first-degree relative with confirmed ovarian cancer. Over the first 2 years, these criteria expanded to include women who had two second-degree relatives with confirmed ovarian cancer, or one first-degree relative with breast cancer and one second-degree relative with ovarian cancer.

Families determined to have a likelihood of more than a sporadic case of the disease are candidates for pedigree expansion in order to determine whether the family demonstrates familial ovarian cancer or contains the patterns to support the diagnosis of a hereditary syndrome. Families with significant clustering of malignant disease are contacted further so that several members can contribute a heparinized blood sample for genetic linkage analysis. Any living relatives with ovarian cancer or related tumors are contacted and asked to contribute a blood sample. Their physicians are notified so that fresh tumor samples can be obtained during any future procedure. Samples of normal ovaries removed during prophylactic oophorectomy are also requested for future study. In addition, paraffin-embedded tumors from deceased family members can be used for linkage analysis.

Patient contact is maintained by personal letters sent after the initial and follow-up visits. In addition, the FOCR publishes a biannual newsletter, *Relatively Speaking*, which deals with registry activities, patient questions, and new information of interest to our registrants.

RESULTS

From April 1991 to July 1993, 137 women from 119 different families enrolled in the Cleveland Clinic's FOCR. The registrants ranged in age from 23 to 73, with a mean age of 43 (*Table 1*). Two patients younger than age 25 were accepted because their sisters were registrants. Eighty percent of our registrants were premenopausal.

TABLE 1
AGE DISTRIBUTION OF REGISTRANTS

Age range	No.	(%)
≤25	2	(1)
26–35	25	(18)
36–45	63	(46)
46–55	28	(20)
56–65	17	(12)
66–75	2	(1)
Total	137	(100)

TABLE 2
DOCUMENTATION OF REPORTED CASES OF OVARIAN CANCER

Type of evidence	No. of cases (%)	
Reported by registrant	171	(100)
Slides reviewed	110	(64)
Pathologic reports reviewed	20	(12)
Total documented cases	130	(76)*

*Only one family undocumented by pathologic study or reports

TABLE 3
NUMBER OF RELATIVES WITH OVARIAN CANCER

Reported number of affected relatives	No. of registrants (%)	
1	97	(71)
2	33	(24)
3	4	(3)
4	2	(1)
> 4	1	(1)
Total	137	(100)

The registrants' pedigrees revealed 171 cases of ovarian cancer in their families. Only one family in the registry lacks documentation of cancer by either review of slides or pathology reports. The documentation is summarized in *Table 2*. Forty of the 137 registrants reported having more than one relative with ovarian cancer. *Tables 3* and *4* summarize the distribution of the affected relatives. The age at diagnosis in the documented cases is shown

TABLE 4
TYPE OF RELATIVES WITH OVARIAN CANCER

Type of relatives affected	No. of registrants	(%)
Only first-degree	97	(71)
Only second-degree	8	(6)
Only third-degree	0	(0)
First- and second-degree	26	(19)
First- and third-degree	4	(3)
Second-and third-degree	0	(0)
First-, second-, and third-degree	2	(1)
Total	137	(100)

TABLE 5
AGE AT DIAGNOSIS IN DOCUMENTED CASES

Age at diagnosis	No.	(%)
≥ 50	95	(73)
40–49	25	(19)
30–39	7	(5)
< 30	3	(2)
Total	130	(100)

TABLE 6
ORAL CONTRACEPTIVE USE AMONG REGISTRANTS

Oral contraceptive use	No.	(%)
Used ≥ 6 months	69	(50)
Used < 6 months	8	(6)
Never used	59	(43)
Information not available	1	(1)
Total	137	(100)

in *Table 5*. The youngest relative with documented ovarian cancer was 21 years old, and the oldest was 85.

Breast cancer was reported in 35% of the families, prostate cancer in 13%, colon cancer in 12%, and endometrial cancer in 4%. There was one family pedigree with a reported history of colon and endometrial cancer as well as carcinoma of the ovary.

Our registrants were queried as to their use of oral contraceptives. This information is listed in *Table 6*.

The initial pelvic examination revealed potential adnexal disease in eight (6%) of our registrants, all of whom were premenopausal. Four had ovarian cysts, three had uterine fibroids, and one had a previously undiagnosed pelvic kidney.

The initial CA125 concentration was high in five patients (all premenopausal), and two of them had abnormal results on a second test. There were no abnormal initial CA125 values in postmenopausal women; however, one patient with abnormal ultrasonographic findings, who ultimately proved to have ovarian cancer, had a value of 42 U/mL on a repeat test.

The ultrasonographic results are summarized in *Table 7*. Studies were evaluated for ovarian size, morphology, and resistive index. All 137 registrants had an initial Doppler vaginal ultrasonographic study.

As shown in *Table 8*, the total cost of all the tests performed was $68 848. Since only one registrant was found to have ovarian cancer, this is our estimated cost to detect one case, and the cost continues to increase as more registrants continue to enroll. To arrive at this total, we estimated the average cost of a 30-to-45-minute examination and discussion, an ultrasonographic study, and a CA125 test. We also added the charges for three repeated CA125 tests and five repeated ultrasonographic studies. In addition, the cost of one exploratory laparotomy (positive for ovarian cancer) and one negative laparoscopy (performed because of persistent elevation of CA125 concentration) are included.

DISCUSSION

We developed the FOCR at the Cleveland Clinic in response to multiple calls from women concerned because someone in their family had ovarian cancer. Our desire to provide some clinical support for these women and our institutional strength in the molecular biology of cancer, we believed, would provide a solid foundation for the registry. Unfortunately, we have been asked to provide the answers to many questions that have yet to be answered. At least within the framework of the Registry, the patients have the information provided in enough depth so they can better appreciate the time line of scientific discovery.

It is important to place this cohort in perspective. They represent a "typical" group of women with a family history of ovarian cancer who are worried and wish to take care of themselves. In fact, the age distribution of the family members with cancer (*Table 5*) is similar to the reported normal age distribution in this disease.[15] Clearly, screening the general population for ovarian cancer is not feasible, owing

to the specificity of the available tests and the low prevalence of the disease.[16] It was hoped that screening a higher-risk population (such as the FOCR) would be more cost-effective than it proved to be. While our costs for the FOCR patients are significantly lower than the average charges for the tests, a group at even higher risk is needed to justify the cost of screening.

TABLE 7
NUMBER OF REGISTRANTS
WITH ABNORMAL RESULTS ON SCREENING VAGINAL ULTRASONOGRAPHY

Group	Size		Morphology		Resistive index	
	Initial	Repeat	Initial	Repeat	Initial	Repeat
Premenopausal	5	2	3	0	6	1*
Postmenopausal	2	1†	1	1†	—	—

*Atypical vessels, resistive index = 45
†Same patient

The patient who proved to have cancer was indeed at high risk (her mother and sister had ovarian cancer). In addition, several other points are interesting in her case. First, her size (170 cm, 121 kg) made pelvic examination difficult, and no abnormality was detected. Second, ultrasonography revealed her left ovary was abnormal in size (22.6 cm^3), morphology (solid-cystic mass), and Doppler tracing (resistive index = 48%). Her CA125 concentration was initially normal but increased to 42 U/mL before surgery. Finally, although the cancer was very limited and easily resected, on exploration she was found to have stage IIIb disease, with peritoneal implants in the right lateral gutter and on the appendix.

TABLE 8
COST PER DIAGNOSED CASE OF OVARIAN CANCER*

Test or procedure	No.	Cost ($)	Total cost ($)
Comprehensive examination	137	195	26 715
Ultrasonographic study	137	150	20 550
CA125 measurement	137	61	8 357
Repeat ultrasonographic study	7	150	1 050
Repeat CA125 measurement	3	61	183
Laparoscopy	1	1 723	1 723
Laparotomy	1	10 270	10 270
Total	—	—	68 848

*One case of ovarian cancer was detected

Future directions

The maturation of this project has resulted in an expanded effort at our institution in the form of a Family Cancer Registry. The FOCR will continue to exist as a subset of the larger registry, and all current registrants will remain in the FOCR. We have elected to narrow the focus, however, and in doing this, have established a three-tiered model.

The first tier will include women older than age 35 who have one first-degree relative with ovarian cancer. This is similar to our earlier criteria, except we have increased the lower age limit. However, we will not require microscopic slides from affected relatives in order for a woman to be seen, counseled, and examined. The focus of the initial first-tier visit will be an examination of the family pedigree. If there is only one first-degree relative with ovarian cancer, the registrant will enter the first tier and undergo a pelvic examination, a CA125 test, and vaginal ultrasonography. These examinations can be repeated on an annual basis as currently recommended; however, they will not be a formal registry function.

If the registrant has any of the following, she will move into the second tier: (1) two first-degree relatives with ovarian cancer; (2) a first-degree relative with ovarian cancer and a second-degree relative with ovarian cancer; (3) a first-degree relative younger than age 50 with breast cancer and a first- or second-degree relative with ovarian cancer; (4) two second-degree relatives with ovarian cancer; or (5) first- or second-degree relatives with ovarian cancer developing before age 40. Other combinations of breast, ovary, uterine, prostate, or colon cancer that demonstrate more extensive family involvement will also qualify registrants for the second tier.

We will try to obtain blood and tissue samples from an adequate number of relatives to perform genetic studies in our research laboratories. Second-tier registrants whose relatives are able to provide these samples (ie, are alive and willing to cooperate) will make up the third tier of the registry, the heart of the genetic research. As we learn more about the genetic transmission of this disease and the best screening methods in these families that are at extremely high risk, we hope to then apply this information to the first-tier registrants.

This new plan is by no means an effort to exclude individuals who would like to be in the registry but have a limited family history. Rather, it is an effort to focus our attention on the highest-risk families so that energy, time, and resources can be applied in areas where we can expect the greatest yield.

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