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Early Detection of Ovarian Cancer: Preliminary Results of the Yale Early Detection Program

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Eighty-four women at high risk for ovarian cancer by having first-degree relatives with epithelial ovarian cancer participated in a newly established, early ovarian cancer detection program at Yale University. Participants were to be evaluated with physical examinations and circulating tumor markers at entry and every six months thereafter. Endovaginal ultrasound and color Doppler flow studies were to be performed at three and nine months following entry into the program. In addition, women were encouraged to follow American Cancer Society guidelines for mammography. Stool was checked for occult blood. Endometrial sampling was offered to post-menopausal women. No participant has developed an ovarian cancer since entering the program. One woman has been diagnosed to have breast cancer. False-positive levels of circulating tumor markers (CA 125, 4/84 [4.8 percent]; lipid-associated sialic acid in plasma, 13/84 [15.5 percent]; NB/70K, 4/84 [4.8 percent]; and urinary gonadotropin fragment, 1/65 [1.5 percent]) were observed on entry into the program. Low resistive indices (<0.5) were documented in 8/91 (8.8 percent) ovaries studied by the color Doppler flow technique. One participant underwent a laparotomy based on a false-positive endovaginal ultrasound examination. Tests now being employed in community practice have a high likelihood of being associated with false-positive results. Therapeutic interventions based on isolated abnormal tumor markers or ultrasound studies obtained from women with family histories of ovarian cancer may lead to inappropriate surgery. It is necessary for cancer centers to develop expertise in ovarian cancer detection techniques to advise physicians in their geographic areas appropriately about the significance of the abnormal screening test.

INTRODUCTION

A program for the early detection of ovarian cancer in a population of women at increased risk for the disease has been established at Yale University School of Medicine. The background and rationale for this program is presented in the preceding article [1]. The specific aims of this program are *(1)* to evaluate a panel of tumor markers and endovaginal ultrasound techniques in women at increased risk for ovarian cancer by virtue of having a first-degree relative (mother, sister) who has had an epithelial ovarian cancer in order to identify which women may actually have

Abbreviations: LSA: lipid-associated sialic acid UGF: urinary gonadotropin fragment

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early-stage ovarian cancer, *(2)* to monitor the value of circulating tumor markers and endovaginal ultrasound studies in order to establish how often these fail by giving false-positive results in the absence of cancer and the clinical strategies to assess the cause of these failures, and *(3)* to identify individuals at high risk for ovarian cancer who may benefit from prophylactic oophorectomy by assessing their personal histories, including medical, nutritional, and personal hygiene habits, their family histories, the levels of circulating tumor markers, the results of endovaginal ultrasound studies and cytogenetic studies. As this program has been active for less than one year, the results presented represent extremely preliminary data.

MATERIALS AND METHODS

The Yale Ovarian Cancer Detection Program began on August 1, 1990. A detailed description of the program is presented in the preceding article [1]. Eighty-four women have completed a family and medical history form and undergone an assessment by a social worker, a physical examination (including pelvic examination) by a gynecologic oncologist, and have had blood and urine obtained for tumor markers and cytogenetic studies. Most have undergone at least one endovaginal ultrasound study, which is performed at three and nine months following entry into the program. Physical examinations and tumor marker studies are performed on entry into the study and at six and 12 months following entry. The time interval for subsequent examinations will be determined after analyzing the first year of the study results. It is anticipated that these examinations will be conducted at less frequent intervals in subsequent program years.

All women entering into the study had blood analyzed for the circulating tumor markers CA 125, lipid-associated sialic acid in plasma (LSA), and NB/70K [2–4]. Sixty-five women had urine assayed for urinary gonadotropin fragment (UGF)[1] [5]. In addition, blood specimens have been stored for subsequent assays for colony stimulating factor 1 (macrophage colony stimulating factor) [6]. All assays presented were performed by Dianon Systems, Inc, a reference laboratory in Stratford, Connecticut. CA 125 assays were performed using a kit from Centocor, Inc., Malvern, Pennsylvania; LSA was assayed using a modification of the technique described by Katopodis et al. [7]; NB/70K was assayed using the method of Knauf [8]. UGF was assayed using kits provided by Triton Diagnostics, Inc. Alameda, California.

Endovaginal ultrasound examination is performed to examine the morphology and vascularity of the ovaries. Endovaginal ultrasound color flow transducers are available on two ATL 9s. A skilled research sonographer and five experienced radiologists dedicated to ultrasound imaging perform and interpret the examinations.

All participants are requested to follow the American Cancer Society guidelines for mammography screening. Pap smears are offered to those women not routinely having Pap smears or those requesting that one be performed. Participants routinely have stool checked for the presence of occult blood. Post-menopausal women are offered the option of endometrial sampling performed to rule out the presence of occult endometrial cancer.

[1]UGF is now commercially available, called UGP (urinary gonadotropin peptide).

TABLE 1
Participants' Characteristics

	No. Patients
Age (Years)	
<35	10
35–39	22
40–44	24
45–49	5
50–54	8
55–59	5
60–64	5
65–69	3
70+	2
Race	
White	82
Black	1
South Asian	1
Blood Type (by History)	
O	12
A	7
B	2
AB	4
Religion	
Protestant	34
Catholic	27
Jewish	20
Russian Orthodox	1
None	2
History of Mumps	
Yes	49
No	28
Uncertain	7
Talc Use for Personal Hygiene	
Yes	45
No	38
Uncertain	1
Tobacco Use[a]	
Yes	40
No	44
Alcohol Use	
Yes	76
No	7
No Response	1

[a]Defined as ever or never used.

RESULT

Participant characteristics are presented in Table 1; only 25 women knew their blood types. Their menstrual and reproductive histories are presented in Table 2. The participants' family history for breast, endometrial, colon, and rectal cancer is shown in Table 3. Seventy-one women had a mother as the first-degree relative with ovarian cancer, nine had a sister, two had a mother and a sister, and two had a

TABLE 2
Menstrual and Reproductive History

	No. Patients
Menarche (Years)	
9	1
10	4
11	9
12	25
13	21
14	8
15	5
16	6
17	1
18	1
Unknown	3
Current Menstrual Status	
Menstruating	62
Post-Menopausal (spontaneous)	17
Surgical Menopause	4
Pharmacologic Menopause	1
Gravidity	
0	14
1	11
2	20
3	15
4	12
5	8
6	2
7	0
8	2
Breast-Fed Children	
0	16
1	8
2	11
3+	11
Non-Applicable	16

mother and a maternal grandmother. The participants' contraceptive history is summarized in Table 4.

To date, none of the participants in this early detection program has developed a carcinoma of the ovary. Three women have, however, undergone laparotomies based on physical findings or laboratory test results. Their histories are briefly summarized as follows:

A 41-year-old nulligravida, whose mother and maternal aunt had each had ovarian cancer, had been having routine semiannual pelvic examinations, by a gynecologist, that were reported to be normal. At the initial physical examination on entry to the screening program, she was found to have a 2 cm irregular nodule along the right side of the uterine corpus. Her initial CA 125 was 27 U/mL, LSA was 21.6 mg/dl, NB/70K was 0, and UGF was 4.1 fm/mg creatinine. She was referred back to her gynecologist, who then confirmed the presence of bilateral adnexal masses by

TABLE 3
Family Cancer History

Relationship	Breast	Endometrial	Colon-Rectal
Self	3	—	—
Maternal			
Mother	6	1	1
Sister	5	—	1
Aunt	14	2	3
Grandmother	4	—	2
Cousin	2	—	—
Great Grandmother	1	—	2
Uncle	—	—	4
Grandfather	—	—	2
Total	32	3	15
Paternal			
Aunt	11	1	3
Grandmother	4	—	—
Uncle	—	—	2
Grandfather	—	—	1
Total	15	1	6

ultrasound examination. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy for what proved to be bilateral ovarian endometriomas.

A 40-year-old gravida 2, para 0, abortions 2, whose mother and grandmother had each succumbed to ovarian cancer, was found to have an abnormal Pap smear (CIN 2–3). She had been followed approximately every six months with pelvic examina-

TABLE 4
Contraceptive History[a]

	Contraceptive Techniques				
Usage Years	Oral Contraceptives	Diaphragm	Condoms	Rhythm	IUD
None	29	47	52	78	65
<1	7	—	2	1	—
1	5	2	5	1	2
2	3	4	—	—	2
3	3	4	3	2	1
4	5	4	1	—	3
5	6	2	2	1	1
6–10	15	3	4	2	8
11–15	3	3	2	—	1
15+	4	7	2	—	1
Unable to quantify years	3	9	12	2	1

[a]Additional forms of contraception: Bilateral tubal ligations, 4; contraceptive foam, 2; husband had vasectomy, 2; contraceptive sponge, 2; withdrawal, 1

tions and Pap smears, all of which had been reported to be normal, including her most recent Pap smear, obtained four months prior to joining the ovarian cancer detection program. Her initial CA 125 was 11 U/mL, LSA was 16.8 mg/dl, and NB/70K was 0. She was referred back to her gynecologist, who confirmed the presence of carcinoma in situ, involving the exocervix and endocervix. She electively underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node sampling (the latter two procedures as part of our surgical staging for possible occult ovarian cancer). No occult cancer was identified.

A 42-year-old nulligravida, whose mother and maternal aunt had each had ovarian cancer, was known to have a multilobulated fibroid uterus. Initial physical examination confirmed the presence of uterine leiomyomata. Serum tumor markers were normal (CA 125 was 18 U/mL, LSA was 11 mg/dl, NB/70K was 0, and UGF was 0.7 fm/mg creatinine). Endovaginal ultrasound studies three months later revealed a 4.5 by 4.9 by 4.2 cm right ovarian cyst with internal echoes, a resistive index of 0.62, and a small amount of free fluid in the cul-de-sac. A follow-up endovaginal ultrasound revealed the cyst to contain solid elements not previously observed, and the fluid in the cul-de-sac had increased. The peak systolic blood flow was noted to be at the level of the systemic circulation. These findings were viewed as compatible with ovarian cancer. Surgery was recommended. The findings at laparotomy revealed that the right ovary was normal, and the imaged mass was a right-sided subserosal uterine leiomyoma.

Four participants had elevated values of CA 125 to 38, 40, 50, and 57 U/mL, the normal value being less than 35 U/mL (Table 5). Three appeared to be secondary to endometriosis, and one preceded by two months the appearance of a benign ovarian cyst. Thirteen participants had elevations of LSA greater than 24 mg/dl, but in each case the CA 125 was normal. Therefore, they are staying in the diagnostic routine established for the first year of the program. Four subjects have had mild elevations of NB/70K to 39, 42, 44, and 506 U/mL, the normal cut-off being 35 U/mL. All of these were associated with LSA greater than 24 mg/dL and normal CA 125 assays, suggesting that the participants might be suffering from inapparent infections rather than an occult malignancy. These participants are remaining in the diagnostic routine established for the first year of the program. One of 65 participants had an elevated UGF (5.1 fm/mg creatinine, the normal cut-off being less than 5 fm/mg).

To date, 91 ovaries have been visualized by endovaginal ultrasound and color Doppler flow studies performed. Eight ovaries (8.8 percent) were associated with a resistive index of less than 0.5, none of which have been associated with an ovarian malignancy (Table 5). These patients continue to be followed on protocol, as none had elevated CA 125 assays (Table 5). In general, repeat color Doppler flow studies have been consistent with the initial studies. The participant with the lowest resistive index, 0.41, has just been reported to have a CA 125 elevation to 88 U/mL. She is currently undergoing additional evaluation.

One participant has been found to have an abnormal mammogram change, biopsy of which proved to be breast cancer. That patient has now undergone a mastectomy and primary breast reconstruction. She is one of four patients (Table 5) who initially had an elevated LSA (30.9 mg/dl) and NB/70K (39 U/mL); however, her tumor marker studies were repeated ten days prior to surgery and all were within normal limits (LSA, 22.2 mg/dl; NB/70K, 12 U/mL; CA 125, 22 U/mL). Five women were found to have occult blood in their stool, and all were sent to their internists for

TABLE 5
Abnormal Imaging and Tumor Marker Assays

Patient No.	Resistive Index: Right Ovary	Resistive Index: Left Ovary	CA 125 (U/mL)	LSA (mg/dl)	NB/70K (U/mL)	UGF (fm/mg)
			CA 125 (Elevated)			
003	N/A[a]	N/A	38	23.1	0	4.7
013	0.53	1.0	50	19.4	0	—
071	0.75	0.55	57	18.6	24	0.2
077	0.50	LSO[b]	40	21.0	5	0.7
			UGF (Elevated)			
034	—	—	15	15.2	0	5.1
			LSA, NB/70K Elevated			
005	1.0	1.0	4	24.7	12	2.5
019	RSO[c,d]	0.57	16	30.9	39	1.1
021	—	—	14	24.7	15	—
026	1.0	1.0	30	24.2	31	—
028	—	—	5	25.4	24	2.8
030	1.0	1.0	17	34.3	42	—
037	—	—	24	24.2	5	0.2
043	1.0	0.67	5	27.7	44	0.9
052	—	—	16	27.2	18	—
058	1.0	0.63	10	25.2	506	2.1
068	1.0	1.0	13	24.4	14	0.6
072	—	—	10	30.3	0	0.1
076	—	—	13	24.5	16	0.9
			Low Resistive Index			
016	1.0	0.49	9	21.7	3	1.4
025	1.0	0.47	9	14.5	0	1.0
054	1.0	0.46	9	23.0	11	0.2
056	0.46	0.41	3	19.0	17	0
060	0.45	0.78	11	15.6	1	—
062	0.44	LSO	21	20.4	32	0.2
081	0.41	1.00	33	18.8	0	0

[a]N/A, Not Available
[b]LSO, Status post-left salpingo-oophorectomy
[c]RSO, Status post-right salpingo-oophorectomy
[d]Patient subsequently diagnosed to have breast cancer

further evaluation. Each occurrence of occult blood in the stool proved to be unrelated to cancer: four were associated with the presence of hemorrhoids and one with recent dental surgery.

A number of findings were either unanticipated or incompletely prepared for, prior to initiating the early detection program. These findings were related to emotional events the participants experienced at having had a mother or sister with ovarian cancer. Our psychological profile of the participants suggested that none had resolved the deaths of their mothers. Interestingly, sisters often had strikingly different views of the nature of their mother's illness. In addition, participants

responded poorly when told that very minor abnormalities of no particular clinical significance were observed on endovaginal ultrasound examinations. The women who had such changes were usually invited to return in a month for reassessment. Despite being assured that this innovation was a change probably reflecting sophisticated new technology rather than suggesting an occult malignancy, at least three patients went from the diagnostic imaging suite to their gynecologists' offices and demanded prompt examinations, as they were certain they had ovarian cancer.

The latter findings required a response. To this end, participants are now better informed about the ultrasound examinations and the possibilities of identifying abnormal changes that almost certainly are of no particular consequence. They are made aware of this fact prior to undergoing the ultrasound examinations. (A similar policy regarding false-positive circulating tumor markers had already been in place.) Participants are informed in advance that, should a small ovarian cyst be identified, they may be asked to take oral contraceptives for one to two cycles to see if the cyst may be suppressed. In addition, our nurses and social workers have been invited to observe endovaginal ultrasound examinations so that they can be more consistent in describing the ultrasound examinations when they interview program participants. Finally, a bimonthly multidisciplinary ultrasound conference has been instituted to review any abnormalities found on endovaginal ultrasound studies in order to be certain that a consistent approach to patient care is practiced for all women participating in this study.

CONCLUSIONS

The existence of this program for only eight months makes drawing any significant conclusions difficult; however, many important observations have been made in a population of women at high risk for ovarian cancer.

The first observation was the intense interest expressed by women who had a mother or sister who had experienced ovarian cancer. We received modest local newspaper converage and local television and radio publicity, yet within a few weeks received more than 1,000 phone calls of inquiry, and identified 285 women who were appropriate for the program. The failure to enter more women into the program is predominantly due to the initial costs, which had to be borne in part by the participants. We have steadily reduced financial charges and have submitted grant applications in an effort to eliminate all financial charges. Women who are unable to pay the costs of this study are accepted without financial obligation.

The second observation was 61 of the 84 (72.6 percent) women participating in this study were under the age of 50 years. While the population participating may seem young, the mean age for women with familial ovarian cancer is 47.7 years, as compared to 59 years for the general population [9,10]. In addition, there is a tendency for women experiencing familial ovarian cancer overwhelmingly to have histologically poorly differentiated serous carcinomas. These malignancies spread rapidly. Successful management requires early recognition. The population studied seems to be appropriate to accomplish our goals.

The third observation related to the emotional fragility women demonstrated when interviewed by an experienced, oncologically oriented medical social worker about their family cancer history. Many women still had unresolved issues of grief and loss. A non-neurotic sense of grief and loss was demonstrated. These issues were

not discussed by patients in a clinical sense, nor did these feelings inhibit daily functioning, but their feelings of loss were very evident in their reminiscences. Women were given an opportunity to discuss their concerns about ovarian cancer and the disruption it created within the family system. Most of the women in the study had never had the opportunity to discuss their grief and loss and welcomed this chance to express emotions and concerns. In many instances, the normal feelings of loss, disruption, and grief were the factors which motivated the women to enter the study. The clinic offers an opportunity for emotional catharsis and also allows women to make intelligent, informed decisions about preventive health care. They are enabled to access health care services via an early detection clinic for ovarian cancer. Moreover, differences in perception regarding their mother's illness were striking among siblings. The latter observation will be the subject of a subsequent report.

Of great concern was the acute anxiety reaction many participants demonstrated when told they had mildly abnormal tests or changes on ultrasound evaluations, using highly sophisticated technology. The anxiety exhibited by the women in this study highlights the need for more intense preparation of the patients. Orientation and education before the initial tests must be increased, and the need for follow-up by staff members at the time of the tests would address the women's anxiety. The anxiety exhibited the intense fear about ovarian cancer and each woman's desperate desire to avail herself of the best medical care possible.

The most important clinical observation regarding ovarian cancer detection was the lack of specificity for all of the early detection techniques used. CA 125, the standard tumor marker most often used for monitoring women known to have ovarian cancer, was elevated above a cut-off of 35 U/mL in four of 84 (4.8 percent) women on entry to the program; LSA was elevated above 24 mg/dl in 13 of 84 (15.5 percent), and NB/70K was elevated above 35 U/mL in 4 of 84 (4.8 percent) of participants. Only one of 65 participants had an elevated value of UGF above 5.0 fm/mg creatinine. UGF was below 5 fm/mg creatinine in three of the four women who had elevations of CA 125 greater than 35 U/mL and in nine patients assayed who had elevated LSA and NB/70K. Endovaginal ultrasound studies were associated with resistive indices of less than 0.5 in eight of 91 (8.8 percent) ovaries studied. Furthermore, one woman was thought to have morphologic ultrasound features compatible with an epithelial ovarian cancer and underwent surgery for this false-positive finding.

Thus, tests which are now being routinely employed by physicians in community practice have a high likelihood of being associated with false-positive results. The preliminary results of this study confirm that therapeutic interventions based on isolated abnormal tumor marker levels or ultrasound examinations from women with family histories of ovarian cancer may lead to inappropriate surgery. It is extremely important to continue accruing women to this study, to evaluate new screening techniques, and to establish similar programs around the United States. It is necessary for clinical cancer centers to develop expertise in detection techniques to advise physicians in their geographic areas appropriately about the significance of the abnormal screening test.

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