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# Early Detection and Screening For Ovarian Cancer

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**Abstract** Ovarian cancer is associated with postmenopausal women of North American or European descent, nulliparous women, and women with a first-degree relative with an epithelial ovarian cancer. Methods for early detection of ovarian cancer are the pelvic examination, ultrasound techniques, and CA-125 monitoring, none of which are highly sensitive or specific for the disease. At the Yale-New Haven Medical Center, first-degree relatives of women with epithelial ovarian cancer were invited to participate in an intense ovarian cancer screening program consisting of tumor markers, endovaginal ultrasound and color Doppler flow studies, and physical examinations performed in a serial fashion. The false-positive rate for the tumor markers varied from 2 to 9% at initial evaluation of the first 247 participants. Endovaginal ultrasound and color Doppler flow techniques were used to evaluate 326 ovaries in 169 women. Resistive indices < 0.5 were present in 26 ovaries (8.4%), and peak systolic velocities > 30 cm/sec occurred in 7 ovaries (2.3%). To date, four breast cancers have been detected, three cervical intraepithelial neoplasias have been identified, and three atypical adenomatous hyperplasias were diagnosed. No epithelial ovarian cancer was found. Isolated screening for ovarian cancer even in high-risk women is not cost effective. Women screened for ovarian cancer should also be evaluated for cancers of the breast, cervix, colon, rectum and endometrium. Isolated abnormal screening test values are not an indication for surgery. 

**Key words:** CA-125, ovarian cancer screening, tumor markers, UGP

Ovarian cancer is the second most common cancer arising in the female reproductive organs in the United States, and the most common cause of cancer death from pelvic reproductive organ sites [1]. The American Cancer Society estimates that in 1995 there will be 26,000 new cases of ovarian cancer and 14,500 deaths [1]. More women will die of ovarian cancer this year than from all other pelvic reproductive organ cancers combined. Ovarian cancer rapidly increases in occurrence after age 40 with the mean age of occurrence at 60 [2]. Epidemiologic factors associated with ovarian cancer, in addition to advanced age, include being of North American or European descent, nulliparous, having a first-degree relative with an epithelial ovarian cancer, and having a personal history of endometrial, colon or breast cancer [3]. Factors associated with a reduced incidence of ovarian cancer include prolonged use of oral contraceptives, multiparity, breast feeding, and tubal ligation [3,4].

## PATHOGENESIS OF EPITHELIAL OVARIAN CANCERS

The most common histologic types of ovarian cancer arise from the surface epithelial cells found on the outside surface of the ovary as well as lining inclusion cysts. Atypical metaplastic changes in these surface epithelial cells may give

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rise to ovarian cancer [5]. "Incessant ovulation" has been associated with the development of ovarian cancer [6]. On the other hand, factors that reduce the number of ovulatory cycles in a woman's lifetime also reduce ovarian cancer incidence, perhaps by reducing inclusion cyst formation. These factors include multiparity and breast feeding; women do not ovulate during pregnancy and for a period after pregnancy. Postpartum anovulation can be prolonged by breast feeding. Furthermore, the use of oral contraceptives suppresses ovulation.

## EARLY DETECTION OF OVARIAN CANCERS

In designing an effective screening test, it is necessary that the disease be of high prevalence, the test must be highly sensitive and specific as well as safe, and it must be readily accepted by patients. Currently, possible tests available for early detection of ovarian cancer include physical examination with palpation of an adnexal mass, serum CA-125 determinations, and pelvic ultrasound examinations.

### Ultrasound Techniques

In 1989, Campbell *et al.* [7] reported on 5,749 women who underwent transabdominal ultrasound screening to detect early ovarian cancers. Three hundred and twenty-six (5.7%) of the women underwent surgery based on this detection technique. Nine women (0.16%) proved to have malignancies involving the ovary; five of these were ovarian cancer (0.09%) and four were metastatic disease from other sites. The five ovarian cancers were Stage I; however, three of the five were tumors of low malignant potential. The cost for each cancer detected has been estimated to be $400,000 [8].

In 1993, DePriest *et al.* [9] reported that 44 of 3,220 (1.4%) women who underwent transvaginal ultrasound examination for early detection of ovarian cancer had adnexal masses requiring surgery. Three (0.09%) of the women were found to have ovarian malignancies, one of which was a granulosa cell tumor. Also in 1993, Bourne *et al.* [10] reported the results of 1,601 women, high-risk by virtue of their family history, who underwent transvaginal ultrasound examinations and color Doppler flow imaging. Sixty-one (3.8%) women required surgery for adnexal masses. Nine (0.56%) proved to have malignancies involving the ovary—six primary ovarian cancers and three metastatic cancers. Five of the six women with ovarian cancer had Stage I disease; however, three of the five had tumors of low malignant potential. The estimated cost per case detected was $70,000 [8]. Of the 10,570 women in these three series who underwent ultrasound assessment for early detection of ovarian cancer, 431 (4.1%) ultimately underwent surgery and 14 (0.13%) had primary ovarian cancers, of which five (0.05%) were invasive epithelial cancers.

### Circulating Tumor Markers

CA-125, a glycoprotein with a molecular weight of approximately 200,000 Daltons, has become the gold standard for ovarian cancer biomarkers [11]. It is elevated in the serum of approximately 80% of women with epithelial ovarian cancer. However, it is only elevated in about 50% of Stage I ovarian cancers [12]. False-positive tests have been associated with the presence of non-ovarian cancers, many common benign gynecologic conditions including fibroids and endometriosis, inflammatory conditions involving the pleura or peritoneum, and cirrhosis [11].

CA-125 has been used in a prospective multi-institutional study in the United Kingdom involving 22,000 postmenopausal volunteers who wished to be screened for epithelial cancer of the ovary [13]. After obtaining CA-125 levels, all women who had values ≥ 30 U/ml were re-evaluated with an ultrasound screening. If the ultrasound was abnormal, the patients would then undergo surgery. CA-125 values < 30 U/ml were found in 21,660 women. Amongst the remaining 340 women, 41 had abnormal ultrasound examinations; 30 were false positives and 11 were true positives. Three of the 11 true positives had Stage I ovarian cancer. This study was a prevalence study; we would expect approximately 25% of women in any large series to have Stage I disease. However, seven women had false-negative results of CA-125 < 30 U/ml, and one had a false-negative result of CA-125 > 30 U/ml, but with a normal ultrasound. All eight women were subsequently found to have ovarian cancer. Surprisingly, five of the eight women were diagnosed with Stage I disease, a disproportionately

high number of Stage I cases apparently not detected through CA-125 screening.

## HEREDITARY OVARIAN CANCER SYNDROMES

Hereditary ovarian cancer syndromes are characterized by clusters of women in two to four generations of the same family with ovarian cancer [14]. These cancers tend to occur in a younger population. Breast-ovarian cancer is the most common hereditary syndrome in which the median age at ovarian cancer diagnosis is 51 years [14]. The second most common syndrome is Lynch Type II or hereditary nonpolyposis colorectal cancer (HNPCC), where the median age for ovarian cancer is 41 years [14]. The site-specific ovarian cancer family syndrome is the least common; women with this syndrome develop ovarian cancer at a median age of 47 years [14].

## YALE EARLY OVARIAN CANCER DETECTION PROGRAM

In August 1990, an ovarian cancer early detection program was initiated at Yale University [15]. Participants are over age 30 and have at least one first-degree relative with an epithelial ovarian cancer. The program first evaluates high-risk women for early stage ovarian cancer using commercially available tumor markers, investigational tumor markers, and endovaginal ultrasound studies including color Doppler flow studies. Second, participants are monitored serially with circulating tumor markers and endovaginal ultrasound examinations to establish the rates of false positivity in the absence of cancer, to develop clinical strategies to assess the cause of these failures, and to determine how often and which tests are best for early detection of ovarian cancer. Third, individuals at high risk for ovarian cancer who might benefit from prophylactic oophorectomy are identified by assessing their personal history, including medical, nutritional, and personal hygiene habits, their family cancer history, circulating tumor marker levels, endovaginal ultrasound studies, and cytogenetic studies. Finally, the psychological aspects of ovarian cancer are assessed in the participants of the screening program.

Women participating in the Yale Early Ovarian Cancer Detection Program complete an extensive personal and family history form prior to entering the Program. Upon acceptance into the Program based on age > 35 years and true family history, they undergo counseling by a medical social worker and nurses trained in gynecologic oncology and ovarian cancer early detection techniques. After a complete history and physical examination by a gynecologic oncologist, they provide blood and urine samples for cytogenetic studies, molecular genetic studies, and tumor markers. The tumor markers include CA-125, lipid-associated sialic acid in plasma (LSA), NB/70K, colony stimulating factor-1 (CSF-1), macrophage colony stimulating factor (MSCF), and urinary gonadotropin peptides (UGP). During the first year, the participants return at 6 and 12 months for an interval history and physical examination, as well as for tumor marker studies. At 3 and 9 months following entry into the Program, the participants undergo endovaginal ultrasound and color Doppler flow studies. In addition, women participating in this study undergo routine Pap smear screening and are encouraged to have baseline mammograms at age 35 and annual mammograms starting at age 40. Stool samples are checked for occult blood. Postmenopausal women who have any abnormal spotting or bleeding are asked to communicate this to us immediately so they can undergo an office endometrial sampling. Women are evaluated at 6 month intervals upon completing the first year.

To date, 247 women have entered into the Program. Their family histories reveal extensive clustering of ovarian and breast cancers among first- and second-degree maternal relatives (332 and 95, respectively), as well as 40 colorectal cancers and 16 endometrial cancers. On the paternal side, only 9 ovarian cancers were identified in first- and second-degree relatives, whereas 34 breast cancers, 29 colorectal, and 3 endometrial cancers were reported. Within the population, 244 women were Caucasian. The median age for sisters at diagnosis of epithelial ovarian cancers was 41 years (range 30–74) and 60 years (range 35–80) for mothers. Ages of participants in the Early Ovarian Cancer Detection Program varied from 28–72 years, with a median of 42.5 years.

On entry into the Program, 22 women (8.9%) had CA-125 elevations > 35 U/ml. Fourteen of 210 women (6.7%) whose UGP was obtained had

creatinine elevations > 4 fmol/ml. Five women had elevations of NB/70K > 35 U/ml (1.6%). Fifteen women had LSA > 24.1 U/dl (6.1%), and none of the first 76 patients sampled had elevations of CSF-1 above 600 U/ml. However, a subsequent evaluation found elevations of this marker in 22% of the women.

CA-125 and UGP were obtained concurrently from 186 participants [16]. One hundred and fifty women were premenopausal and 32 were postmenopausal. Eighteen premenopausal women had an elevated CA-125 (range 37–283 U/ml, median 48 U/ml). None of the women had concurrent elevations of UGP. Evidence of uterine leiomyomata was found in 8 of the 18 women by physical examination or endovaginal ultrasound examination. One of 32 postmenopausal women had a CA-125 elevated to 47 U/ml, and she, too, had a uterine leiomyoma. Only one postmenopausal patient had mild elevations of CA-125 (38 U/ml) and UGP (4.7 fmol/ mg creatine). Serial levels of CA-125 and UGP were obtained on 105 women [16]. Seventy of the 105 women had normal values throughout their participation in the Program.

Initial ultrasound examinations have evaluated 326 ovaries in 169 women to date. Ovaries in 47 of 262 menstruating women (17.9%) had no detectable flow, compared to 15 of 48 (31.3%) ovaries in postmenopausal women. Ten of 262 ovaries (3.7%) could not be identified in the menstruating group, and 6 of 54 ovaries (11.1%) in postmenopausal women could not be detected. Resistive indices (RI) less than 0.50 were found only in 26/262 premenopausal ovaries (9.9%). The peak systolic velocity was elevated above 30 cm/sec in 6 of 262 premenopausal ovaries (2.3%) and 1 of 48 postmenopausal ovaries (2.1%). Only one woman in the entire series was thought by ultrasound morphologic and color Doppler flow evaluation to have ovarian cancer. At surgery, the woman proved to have a 7 cm subserosal pedunculated fibroid.

The entire series has detected four new breast cancers; one woman developed recurrent breast cancer. In addition, three women with cervical intraepithelial neoplasia were identified. Three of 31 postmenopausal women were found to have atypical endometrial hyperplasia. No one has been found to have an invasive epithelial ovarian cancer.

Results of these studies lead us to conclude that isolated screening for ovarian cancer even in high-risk women is not cost effective. Women screened for ovarian cancer should also be evaluated for cancers of the breast, cervix, colon, rectum, and endometrium. Screening tests currently available for epithelial ovarian cancer have a 2–9% false-positive rate. Isolated abnormal test values are not an indication for surgery. Failure to identify an ovarian cancer in this group of high-risk women suggests that the value of prophylactic oophorectomy in women with first-degree relatives with this disease remains to be proven.

Recent advances in molecular diagnostic techniques led to isolation of the BRCA1 gene as a potential screening tool for women from breast-ovarian cancer syndrome families at high risk of developing ovarian cancer [17]. With over 80,000 base pairs, numerous mutations are possible within this gene [18]. While the mutations are consistent within a family with hereditary ovarian cancer syndrome, they may differ from one family to the next. Another two years are anticipated before this gene will be ready for clinical testing. Mutations of the *mut*S homology gene in HNPCC patients have been reported [19]. Screening tests will be available for women who have HNPCC family histories.

Currently, our management strategies for women with inherited susceptibility to ovarian cancer include surveillance with serial pelvic examinations, ultrasound monitoring, and CA-125 determinations. Prophylactic oophorectomy can be used, but unfortunately women may develop intraabdominal carcinomatosis indistinguishable from ovarian cancer despite the fact that they have had their ovaries removed [20]. Chemoprevention may be the most appropriate approach for women with inherited susceptibility to cancer; birth control pills seem to statistically reduce the incidence of the cancer in the population as a whole, but no data exists as to whether prolonged oral contraceptive use is a valid strategy to reduce ovarian cancer risks for women with inherited forms of epithelial ovarian cancer.

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