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REVIEW ARTICLE

Epithelial ovarian cancer. Risk factors, screening and the role of prophylactic oophorectomy

Daniilidis A, Karagiannis V

3rd Dpt of Obstetrics and Gynaecology, Hippokration Hospital, Thessaloniki, Greece

Abstract

Epithelial ovarian cancer is the seventh most frequent cancer in European women. Many theories have been postulated regarding the pathogenesis of ovarian cancer. Risk factors are not well defined, with the exception of low parity and oral contraceptive use. Approximately 10% of ovarian cancer are hereditary, with BRCA1 and BRCA2 explaining the majority (approximately 90%) of hereditary ovarian cancer cases. The lifetime risk varies between 15 and 66%, suggesting the existence of modifying genetic or environmental factors. Family history can be used to define women who are at increased risk of ovarian cancer. Individuals at high risk are those with a first degree relative (mother, father, sister, brother, daughter or son) affected by cancer. It must be noted that currently available tests do not attain the aforementioned high level of sensitivity. Evidence suggest that presymptomatic screening by grey scale ultrasound (with or without Doppler), CA125, pelvic examination, or combinations of these, are not effective in detecting tumors at an early stage. Women identified as being at high risk of ovarian cancer can be offered prophylactic oophorectomy. The decision whether or not to proceed to prophylactic oophorectomy is influenced by the fact that most women at increased risk of ovarian cancer are also at increased risk of breast cancer and there is evidence that oophorectomy reduces breast cancer in these cases. *Hippokratia 2007; 11 (2): 63-66*

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Corresponding author: Daniilidis A, 81 A Nimfeou, 54224, Thessaloniki, Greece, tel: + 306932211395, e-mail: angedan@hotmail.com

Epithelial ovarian cancer is the seventh most frequent cancer in European women, with 58000 new cases and 38000 deaths only in 1995 [1]. The incidence is low under the age of 40 years but increases rapidly after menopause.

Despite new chemotherapy agents, the prognosis remains fairly poor with a 5-year relative survival of 30% [2]. The survival rate of women with early-stage ovarian cancer is significantly higher than in women with advanced-stage disease. Unfortunately, the vast majority of women with ovarian cancer are diagnosed with advanced disease. Retrospective studies show that women with ovarian cancer present with non-specific symptoms including abdominal pain and bloating; changes in bowel habit, urinary and/or pelvic symptoms[3-5]. Cachexia is uncommon and women with advanced disease often look surprisingly well. Most women with ovarian cancer present with advanced disease. Patients who present with non-specific gastrointestinal symptoms may be misdiagnosed as suffering from irritable bowel syndrome.

Many theories have been postulated regarding the pathogenesis of ovarian cancer. Risk factors are not well defined, with the exception of parity and oral contraceptive use. Most theories concider the epidemiology of epithelial ovarian cancer, representing approximately 90% of all ovarian carcinomas.

This paper reviews recent studies on risk factors, screening and the value of prophylactic oophorectomy in high risk women for ovarian cancer.

Risk factors

Reproductive factors

The protective effects of increasing parity and breast feeding have been clearly established[6]. Early age at menarche and late age at menopause increase the risk of ovarian cancer only modestly, so that it can be assumed that the length of menstrual life plays no crucial role in the pathogenesis of the disease[7]. The risk of sub/infertility on the risk of ovarian cancer has been extensively studied. Most studies use attendance at an infertility clinic as a marker for subfertility. The difficulty is the differentiation between the infertility itself and the treatment given at the clinic that may itself increase the risk of ovarian cancer. A pooled analysis of case-control studies, including 5207 cases and 7705 controls, suggested that specific biological causes of infertility, like endometriosis, rather than fertility drugs increased the risk of ovarian cancer [8].

Oral contraceptives

Several studies have consistently shown a decreased risk of sporadic as well as familial ovarian cancer with the use of oral contraception [9]. The risk reduction is already apparent after a few months of use and persists for years after discontinuation. Low-dose formulations (<35μg

ethinyl oestradiol) also confer a substantial risk reduction [10]. However, inconsistent results were reported for women at risk of hereditary ovarian cancer. Although a case-control study in 207 BRCA heterozygotes[11] reported a significant 50% risk reduction, a case-control study in Jewish women[12] found that oral contraceptives significantly decreased the risk of ovarian cancer only in non-carriers but not in carriers of a BRCA mutation.

Oestrogen/hormone replacement therapy

Hormone replacement therapy (HRT) has been inconsistently linked to ovarian cancer. Recently, several prospective studies[13, 14] consistently found a small increase of the risk, especially for long-term users of oestrogen replacement therapy. Intermittently rather than continuously added progestins might further increase the risk[15].

Diet

The evidence remains inconsistent; recent studies suggest that food items high in carotene and lycopene might decrease the risk[16], whereas red meat was associated with an elevated risk[17]. However, all positive studies were case-control studies, and a recent prospective study found no association between the use of vitamins/carotenoids and ovarian cancer[18]. It might be that (part of) the reported associations in previous studies were caused by the various types of bias (especially recall bias) that can occur in case-control studies.

Physical activity

It is hypothesized that recreational physical activity may reduce the risk of ovarian cancer by decreasing oestrogen levels. However, although this reduced risk was found by several studies, others found no or even a modest positive association. The most recent study[19] with 327 cases and 3129 controls, reported a small non-significant, decrease in risk only for the highest category of recent vigorous activity.

Use of non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs increase apoptosis in ovarian cancer cell lines and can inhibit ovulation[19]. In observational studies, the association between commonly used anti-inflammatory drugs and ovarian cancer remains unclear. A Danish cohort study found no evidence of a protective effect of paracetamol[20], and a case-control study conducted in the USA concluded that, although non-significant, the observed risk estimates appeared to be compatible with a small decrease of risk by regular (more than three times a week for a period of at least 6 months) aspirin use[21].

Hereditary ovarian cancer

In most cases risk estimates are based on a family history. The lifetime risk estimate for individuals who have one first degree relative with ovarian cancer is two to five times the population risk[22, 23]. Evidence regarding the lifetime risk when an individual has more than one affected relative is sparse but this is estimated at 3 to 23%[22, 23]. Two types of ovarian cancer susceptibility genes have been identified: the breast and ovarian cancer tumour suppressor genes (BRCA1 and BRCA2) and the mismatch repair genes associated with Hereditary Nonpolyposis Colorectal Cancer (HNPCC) families[24]. Mutations in the BRCA1 gene are estimated to confer a 30% lifetime risk of ovarian cancer up to age 60 years and mutations in BRCA2 gene are estimated to confer an ovarian risk of 27% up to age 70 years[22, 25]. The mismatch repair genes confer an increased lifetime risk of ovarian cancer of approximately 9 to 12% in addition to an increased risk of endometrial cancer[26, 27].

Approximately 10% of ovarian cancer are hereditary, with BRCA1 and BRCA2 explaining the majority (approximately 90%) of hereditary ovarian cancer cases. The lifetime risk varies between 15 and 66%, suggesting the existence of modifying genetic or environmental factors[28].

Screening for ovarian cancer

To be suitable for screening, a disease must have a significant prevalence and be a significant cause of mortality. There must be a preclinical phase that can be detected, and the disease must be amenable to therapy. The screening test itself must have sufficient specificity, sensitivity, and positive predictive value (PPV) to be effective, and it must be cost-effective. In ovarian cancer, if one assumes a prevalence of 50/ 100000, a test with 99% specificity and 100% sensitivity would yield only 1 in 21 women with a positive screen actually having the disease (i.e. PPV= 4.8%). It must be noted that currently available tests do not attain the aforementioned high level of sensitivity.

Family history can be used to define women who are at increased risk of ovarian cancer [29]. Individuals at high risk are those with a first degree relative (mother, father, sister, brother, daughter or son) affected by cancer within a family that meets one of the following criteria:

- two or more individuals with ovarian cancer, who are first degree relatives of each other
- one individual with ovarian cancer at any age, and one with breast cancer diagnosed under age 50 years, who are first degree relatives of each other
- one relative with ovarian cancer at any age, and two with breast cancer diagnosed under 60 years, who are connected by first degree relationships
- known carrier of relevant cancer gene mutations
- untested first degree relative of a predisposing gene carrier
- an individual with both breast and ovarian cancer
- three or more family members with colon cancer, or two with colon cancer and one with stomach, ovarian, endometrial, urinary tract or small bowel cancer in two generations. One of these carriers must be diagnosed under the age of 50 years.

Potential screening tests for ovarian cancer include the bimanual pelvic examination, serum CA 125 and ultrasound imaging. One systematic review[30] and three small cohort studies [31-33] suggest that presymptomatic screening by grey scale ultrasound (with or without Doppler), CA125, pelvic examination, or combinations of these, are not effective in detecting tumors at an early stage. The pelvic examination, which can detect a variety of gynecological disorders, is of unknown sensitivity in detecting ovarian cancer. Although pelvic examinations can occasionally detect ovarian cancer, small, early- stage ovarian tumors are often not detected by palpation due to the deep anatomic location of the ovary. Thus, ovarian cancers detected by pelvic examination are generally advanced and associated with poor survival. The pelvic examination may also produce false positives when benign adnexal masses are found.

Tumor markers have limited specificity. Measurement of serum CA 125 is the blood test most widely used to detect ovarian cancer. CA 125 is a glycoprotein antigen. Approximately 80% of patients with advanced ovarian cancer have elevated concentrations of CA125. A maximum of only 50% of patients with clinically detectable stage I disease have elevated CA 125 levels. Elevated concentrations of CA125 are associated with malignant tumors of the pancreas, breast, lung, colon and ovary. Menstruation and benign conditions such as endometriosis, pelvic inflammatory disease, liver disease and recent laparotomy can also be associated with elevated CA125 levels. Despite its poor sensitivity and specificity, CA 125 is most useful for detecting and monitoring non- mucinous epithelial tumours of the ovary. Limited data are available on the potential benefit of screening with serum CA 125 in women at inherited risk of ovarian cancer. No clear evidence was identified as to whether screening in high risk groups has an impact on mortality from ovarian cancer. Ultrasound imaging has also been evaluated as a screening test for ovarian cancer. Transvaginal ultrasound (TVS) is currently the preferred modality, since it is able to estimate ovarian size, detect masses as small as 1cm, and distinguish solid lesions from cysts. Transvaginal color- flow Doppler ultrasound can also identify vascular patterns associated with tumors. However, specificity of ultrasonography is not adequate for use as a single screening modality. In screening studies, the reported sensitivity and specificity of transabdominal or transvaginal ultrasound were 50-100% and 76-97% respectively. Studies have shown that routine ultrasound testing of asymptomatic women has a low yield in detecting ovarian cancer and generates a large proportion of false-positive results that often require diagnostic laparotomy or laparoscopy[34].

There is no evidence to support routine screening with any of the available methods in asymptomatic women. Given the risks, inconvenience, and substantial costs of follow-up testing, and the current lack of evidence that screening reduces morbidity or mortality from ovarian cancer, routine screening cannot be recomented. Screening may be appropriate for women whose family history suggests hereditary ovarian cancer syndrome, due to very high risk of cancer in this disorder.

Role of prophylactic oophorectomy

Women identified as being at high risk of ovarian cancer can be offered prophylactic oophorectomy. The decision whether or not to proceed to prophylactic oophorectomy is influenced by the fact that most women at increased risk of ovarian cancer are also at increased risk of breast cancer and there is evidence that oophorectomy reduces breast cancer in these cases[35].

A woman with one first-degree relative with ovarian cancer has a lifetime risk of ovarian cancer about 5%. This is probably not high enough to warrant prophylactic oophorectomy as an independent operative procedure with its attendant risks. The probability of a hereditary ovarian cancer syndrome in a family pedigree increases with the number of affected relatives, with the number of affected generations and with young age of onset of disease. Therefore, prophylactic oophorectomy should be considered in these settings with careful weighing of the risks and potential benefits. Prophylactic oophorectomy performed in women undergoing abdominal surgery for other indications such as benign uterine disease is also associated with a significant reduction in the risk of ovarian cancer. However, estrogen replacement therapy should be discussed with the patient prior to the procedure.

The risk of ovarian cancer in women from families with hereditary ovarian cancer syndromes is sufficiently high to recommend prophylactic oophorectomy. Two complementary studies in BRCA 1/2 heterozygotes demonstrated that prophylactic oophorectomy can reduce the risk of hereditary ovarian cancer as well as breast cancer. In a prospective study of 170 carriers with a mean follow up of 2 years[34], one woman developed peritoneal cancer and three breast cancer in the salpingo-oophorectomy group of 98 women. Three occult stage I gynaecological tumours were found at the time of prophylactic surgery. In the surveillance group of 72 women, five women developed ovarian or peritoneal cancer and eight developed breast cancer. The combined hereditary risk (HR) for ovarian cancer was 0.25 (95% CI 0.08- 0.74). In a multicentre retrospective study with a mean follow-up of almost 9 years[36], 58 out of 292 carriers opting for surveillance developed ovarian cancer. Among 259 women undergoing prophylactic oophorectomy, two women developed primary peritoneal cancer (HR 0.04; 95% CI 0.01- 0.16). In six women a stage I ovarian cancer was diagnosed at the time of surgery. Breast cancer was diagnosed in 60 out of 142 women opting for surveillance compared with 21 out of 99 women in the oophoretomy group, giving an HR of 0.47 (95% CI 0.29- 0.77).

The risk-reducing potential of tubal ligation had already been shown in sporadic ovarian cancer. In addition, a matched case-control study in 232 BRCA heterozygotes

with ovarian cancer and 232 carriers without the disease[37] showed that the adjusted odds ratio of developing ovarian cancer was 0.39 (P=0.002) after tubal ligation. The biological mechanism is unclear. Hypothesis include the reduction of ovarian blood supply or a decreased retrograde transport of potential carcinogens through the fallopian tubes.

Conclusions

Standards of care of ovarian cancer are determined on the basis of all clinical data available for an individual case and are the subject to change as scientific knowledge and technology advance and patterns of care evolve. The ultimate judgement regarding a particular counseling, clinical procedure or treatment plan must be made by the doctor, following discussion of the options with the patient, in the light of the diagnostic and treatment choices available.

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