SCREENING AND PROGNOSTIC FACTORS FOR OVARIAN CANCER

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ABSTRACT

Ovarian cancer is one of the neoplastic gynecological diseases that is the most difficult subject to screening. This is the reason that most newly-diagnosed cases are at III-IV FIGO stage. The lack of an appropriate screening method affects the oncologic results and, therefore, the ovarian cancer presents with the worst prognosis of all neoplasms of female reproductive organs. This review attempts to discuss some methods for early diagnosis of ovarian cancer, especially in cases with adnexial formation. The prognostic factors in the literature available influencing on patients' survival and treatment outcomes are considered.

Key words: *ovarian cancer, screening, transabdominal ultrasonography, prevention, prognostic factors*

Peak incidence rate of the invasive epithelial ovarian carcinoma is at 56 and 60 years of age (6,30,35). This incidence increases steeply from 20 to 80 years of age (30). Fewer than 1% of such cancers occur before the age of 21 years, and two-thirds of ovarian malignant tumours in this age are germ cell tumors (29,30,35). About 30% of ovarian neoplasms in postmenopausal women are malignant, whereas only about 7% of ovarian epithelial tumours in premenopausal patients are malignant (6,35).

Ovarian carcinomas are associated with low parity and infertility (28). Early menarche and late menopause increase the risk of ovarian cancer (11). These facts and the relationship with parity and infertility have led to the hypothesis that suppression of ovulation may be an important factor. Theoretically, surface epithelium undergoes repetitive disruptions and repair. This process can lead to possible spontaneous mutations and the occurrence of oncogenic phenotype.

The performance of prophylactic oophorectomy reduces, but does not completely eliminates the risk of ovarian cancer (31,38). As the entire peritoneum is at risk, peritoneal carcinomas can occur even after prophylactic oophorectomy. As the ovaries provide protection from cardiovascular and orthopedic diseases, the above mentioned intervention should not be routinely used in premenopausal women at low risk for ovarian cancer.

The value of tumour markers and ultrasound examination for screening of epithelial ovarian cancer is not clearly established by prospective studies. Screening results with transabdominal ultrasonography are encouraging (7,16,39), however, specificity is limited. The progress in transvaginal ultrasonography contributes to the very high sensitivity (95%) of the method for detection of ovarian cancer at an early stage, however, the use of this test alone as a screening method allows a performance of 10-15 laparotomies for each case of detected cancer (7,16).

There are disappointing results from routine annual pelvic examination about the early detection

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of ovarian cancer (33). Transvaginal colour-flow Doppler assessment of ovarian vessels is useful as a supplemental test to ultrasonography (24,25), but not for screening purposes.

CA 125 has proven its role in the early diagnosis of epithelial ovarian cancer (10,18,19,34,39-41). CA 125 can detect 50% of patients with stage I disease and 60% of patients if those with stage II are included (34). CA125 specificity can be improved when combined with transvaginal ultrasonography (20) or if CA125 levels are followed-up over time. These data enhance the implementation of prospective screening studies in Sweden and the United Kingdom (10,19). In them, patients with elevated CA125 levels (> 30 U/mL) have undergone abdominal ultrasonography and 14 ovarian cancers are diagnosed among 27,000 women screened. About four laparotomies are performed for each case of cancer detected.

In a randomized trial of 22,000 women aged 45 years or older in the UK (20), the patients are divided into a control group of routine pelvic examination (10,977) and a screening group (10,958). The screening consists of annual measurement of a serum CA125 levels, pelvic ultrasonography if the CA125 is 30 U/mL or higher, and referral to a gynecologist if the ovarian volume is 8,8 mM or greater on the ultrasonography. Of the 468 women from the screening group with an elevated CA125, 29 are referred to a surgeon, six cancers are established, 23 females present with a false-positive screening result, which means a positive predictive value of 20,7%. During the 7-year follow-up period, cancer develops in 10 additional women from the screened group, as it does in 20 women from the control one. Although survival in women with cancer in the screened group is 72,9 months compared with 41,8 months in the control one, mortality rate does not differ significantly between these groups (18/10977 versus 9/10958; relative risk 2,00). Therefore, multimodal approach for screening of the ovarian cancer is feasible, however, a more comprehensive trial is needed to assess its effect on mortality.

Given the false-positive results for both CA125 and transvaginal ultrasonography, particularly in premenopausal women these tests are not cost-effective and should not be used routinely for screening purposes.

Genetic risk for epithelial ovarian carcinoma

The lifetime risk of ovarian cancer for women in the United States is about 1,4% (6,35).

The risk of ovarian cancer is higher in women with a certain family history compared with that of the general population. Most epithelial cancers are sporadic with familial or hereditary forms being 5-10% of all malignant tumours.

Hereditary ovarian cancer

Most hereditary ovarian carcinomas are associated with mutations in the BRCA1 gene located on chromosome 17. A small proportion of inherited disease is due to another gene, BRCA2, located on chromosome 13. These two genes are associated with genetic predisposition to both ovarian and breast cancer.

Prevention

As parity is inversely related to the risk of ovarian cancer, having at least one child has a protective effect on the disease and reducing the risk from 0,3 to 0,4. Oral contraceptive use reduces the risk of epithelial ovarian cancer (28). Women who use oral contraceptives for 5 or more years diminish their relative risk to 0,5 (50% reduction in the likelihood of development of ovarian cancer). Women with two children and oral contraceptive usage for 5 years or more present with 70% risk reduction (12). Therefore, the oral contraceptives are the only documented method of chemoprevention for ovarian cancer and it should be recommended for this purpose. This is important, especially in patients with family history of ovarian cancer.

Fenretinide (4-hydroxyretinoic acid), a derivative of vitamin A, is given to women with unilateral breast cancer in an effort to reduce the risk of contralateral breast cancer. In a prospective, randomized, placebo-controlled study in Italy (9), fenretide or placebo are administered for 6 months in women with unilateral breast cancer. In the group with fenretinide, no ovarian cancer develops at all, whereas six cases are registered in the control group.

Prognostic factors

Treatment outcome can be assessed on the basis of prognostic factors which are divided into pathological, biological and clinical (23).

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Pathological factors

The morphological and histological patterns, including the architecture and grade of the lesion, are important prognostic variables (6). The histological type is of no prognostic value. However, it is recently suggested that clear-cell carcinomas are associated with a worse prognosis than other histological types (23,41).

The histological grade determined by the degree of differentiation, the extent of the cellular anaplasia and the presence of undifferentiated cells are of prognostic significance. Because of the great subjectivism in grading estimation (1,15), however, its value as prognostic factor is not clearly established yet (23,41). Baak et al. (2) propose a standard grading system based on morphometric analysis that correlates with prognosis, especially due to its capacity to distinguish low-grade or borderline tumours from other neoplasms.

Biological factors

Several biological factors are associated with the prognosis of epithelial ovarian cancer. Using flow cytometry, it has been shown that ovarian cancers are aneuploidy (13) and there is a significant relationship between ploidy and FIGO stage. Early-staged cancers tend to be diploid while highly staged ones tend to be aneuploid (13,32). The patients with diploid tumours have a significantly longer median survival than those with aneuploid tumours of five years versus one year, respectively (13). Multivariate analysis shows that ploidy is an independent prognostic factor and one of the most important predictors of survival (13).

More than 60 proto-oncogenes are already identified, and research focuses on amplification or expression of these genetic loci and their role in the development and progression of ovarian cancer (4,5). Some 30% of epithelial ovarian tumours express HER-2/neu oncogene and this group is of a poor prognosis, especially concerning the patients with more than five copies of the gene (37). A similar incidence rate (of 32%) of HER-2/neu gene expression is reported, too (3). The patients with such a gene expression have a shorter survival (15,7 versus 32,8 months). Other authors do not confirm these findings (26,27). A literature review (26) reveals an overall incidence rate of HER-2/neu expression only about 11%. Thus the prognostic value of HER-2/neu expression in ovarian cancers remains unclear and requires further research.

p53 is the most commonly expressed tumour suppressor gene in ovarian carcinoma (14,17). Moreover, about half of all epithelial ovarian cancers have mutations in the p53 in the tumour.

Clinical factors

In addition to staging, the size of residual tumours after primary surgery, the volume of ascites, and patient's age are independent prognostic factors (8,21,22,36,40). Among the patients with stage I disease, a multivariate analysis shows that grading and the dense adhesion of the tumour to the pelvic peritoneum exert a significant adverse effect on the prognosis, whereas intraoperative tumour spillage or rupture do not worsen the prognosis (8). Ovarian cancers that undergo intraoperative rupture or decomposition do not worsen the prognosis, whereas tumours ruptured preoperatively have a poorer prognosis (36). A multivariate analysis demonstrates that tumour grading, capsular penetration, surface growths and malignant ascites rather than any iatrogenic rupture are poor prognostic variables for early-stage ovarian cancers (40).

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