Archives of Oncology and Cancer Therapy

Volume 1, Issue 1, 2018, PP: 54-58

Prevention of Ovarian Cancer among High-Risk Women

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Abstract

Ovarian cancer is highly lethal malignancy diagnosed at the late stage because of generalized non-specific symptoms. Exact etiology of ovarian cancer is complex and not known completely. Most prominent risk factor is family history of the ovary and breast cancer. 5-15% of ovarian cancers are associated with mutations of BRCA1, BRCA2 and mismatch repair genes. Some possible protective factors are the use of oral contraceptives for prolonged duration, pregnancy, tubal ligation and hysterectomy. Identification of high-risk women for development of ovarian malignancy is difficult because of scarcity of knowledge about early ovary carcinogenesis and any premalignant condition. Serum CA-125 estimation and trans-vaginal ultrasound (TVUS) have been tried for screening purpose, but they are not reliable tests.

Chemoprevention and prophylactic surgery are emerging as potential preventive measures to reduce the risk of ovarian cancer. High-risk women, who have not satisfied parity, cannot opt primary prevention of ovarian cancer by bilateral oophorectomy. Oral contraceptives, fenretinide, non-steroidal anti-inflammatory drugs and some natural compounds are under evaluation as chemopreventive agents with controversial reports. To achieve acceptable benefit to risk ratio, identification of women at high-risk of ovarian cancer and providing them chemoprevention with minimal adverse effects is challenging task.

Keywords: *ovarian cancer, risk factors, chemoprevention.*

Background

Chemoprevention of ovarian cancer remained an unexplored area in experimental as well as clinical research area. Ovarian cancer is the highly lethal malignancy diagnosed at the late stage because of generalized non-specific symptoms. Its prognosis is poor with 5-years survival rates of about 40%. (1) Data from different studies suggest every year addition of 238100 new cases and 151900 ovarian cancer-related deaths worldwide making ovarian cancer as 8th dangerous cancer among women. (2) Epithelial ovarian cancer (EOC), the most common type of ovarian cancer is a heterogeneous clinical entity. It constitutes about 80-90% of the ovarian cancers with different histologic types, each with unique molecular signatures. (3) Ovarian cancer is a devastating fatal disease with limitations of detection at an early stage and lack of effective preventive strategies. The lifetime risk of ovarian cancer is 1.4% in the general population, while women with hereditary ovarian cancer syndromes have 25-60% for developing epithelial ovarian cancer. (5) Hence, effective prevention and early detection of ovarian cancer remains an important task among high-risk women.

Risk Factors and Screening Tools for Ovarian Cancer

Exact etiology of ovarian cancer is not known. Some identified risk factors for developments of ovarian cancers are increased age, late childbearing, obesity infertility and medications for fertility and family history of ovarian cancer, previous breast cancer and use of only estrogen for long period, endometriosis. Most prominent risk factor is family history of the ovary and breast cancer. Approximately 5-15% of ovarian cancers are familial and associated with mutations of BRCA1, BRCA2 and mismatch repair genes. (5) Women with BRCA2 mutations carry 39%,

and those with BRCA1 mutations carry 22% lifetime risk of developing ovarian cancer. (6) Hereditary ovarian cancer syndrome is the condition having at least two first-degree relatives with epithelial ovarian cancer and have 13-50% risk for ovarian cancer. Women with Lynch syndrome have 3-14% risk of ovarian cancer. (4)

Some possible protective factors are the use of oral contraceptives for prolonged duration, pregnancy, tubal ligation and hysterectomy. Relative risk of ovarian cancer reduces by about 20% with 5 years of use of OCP and halved with 15 years use. (7) Epidemiological studies and recent advances in molecular biology propose incessant ovulation and gonadotropin mechanism to play central role in the causation of ovarian cancer. Salehi F and associates reviewed hormonal risk factors for ovarian cancer and with emphasis on hormonal factors. They suggested some factors implicated in the etiology of the disease like ovulation, gonadotropic and steroid hormones, depletion of germ cells, oncogenes, tumor suppressor genes, cytokines, growth factors and endocrine disruptors. (8) The role of inflammation also has been proposed as the contributor in the pathophysiology of development of ovarian cancer. It might cause cell damage, oxidative stress and release of cytokines and prostaglandins, which may be mutagenic. (9) Still the etiology is not clear and needs future strong evidences to link such risk factors with ovarian cancer.

Identification of high-risk women for the development of ovarian malignancy is difficult because of scarcity of knowledge about the early ovary carcinogenesis and any premalignant condition. Hence, it can be done from clinical ground only and family history has been identified as the most important risk factor for ovarian cancers. Progestin is under evaluation for chemoprevention of ovarian cancer. But there are chances of increased risk of breast cancer with progestin. Carriers of BRCA mutations can be targeted for primary prevention of ovarian cancer by prophylactic salpingo-oophorectomy. But early menopause is the chief concern related to this option of surgery. (3)

Biology of ovarian cancer is complex and still incompletely understood. Hence, there is an urgent need of the research to understand the complete pathophysiology, risk factors and advanced screening technologies in the field of ovarian chemoprevention. Recently fallopian tubes have been suggested as the site of origin for the high-grade serous ovarian carcinoma, the most common and aggressive histotype of epithelial ovarian cancer. It is associated with hereditary breast and ovarian cancer syndrome. Hence among high-risk women, risk reducing surgical removal of ovary and fallopian tubes has been recommended that should be completed in post-childbearing period by the age of 35-40. (10)

Only two tests are available as screening tools for ovarian cancer. Serum CA-125 estimation and trans-vaginal ultrasound (TVUS) have been tried for screening purpose, but they are not reliable tests. Early detection of ovarian cancer needs tests with high sensitivity (>75% for stage I) and very high specificity (>99.6%) to gain more than 10% positive predictive value. Some researchers obtained these criteria fulfilled by TVUS, but major limitation remains cost for annual screening. Two-steps protocol can be implemented for screening like first estimation of serum CA-125 concentration to calculate risk and then refer high-risk women to TVUS. Considering poor outcome of ovarian cancer, investigators utilized different approaches to discover potential specific and sensitive markers that can be used alone or in combination with CA125. Some of them under evaluation are mesothelin, M-CSF, osteopntin, kallikrein and soluble EGF receptors. (11)

Chemoprevention in Ovarian Cancer

Ovarian cancer is a leading cause of gynecological cancer related deaths. To achieve acceptable benefit to risk ratio, identification of women at high-risk of ovarian cancer and providing them chemoprevention with minimal adverse effects should be the goal. More the numbers of ovulatory cycles, greater are the risk for ovarian cancer. Hence the factors that decrease the number of ovulatory cycles, including repeated pregnancies, breast-feeding for prolonged duration and use of oral contraceptives confer protection against ovarian cancer. Chemoprevention and prophylactic surgery are emerging as potential preventive measures to reduce the risk of ovarian cancer. Prolonged use of oral contraceptives (5 years) reduces ovarian cancer risk for 10 years even after discontinuation. By decreasing frequency of ovulations, oral contraceptives decrease mutagenic effects of cell proliferation and entrapment of ovarian epithelium within stroma. (12) There is compelling evidence establishing protective effects of oral contraceptives in reducing risk for ovarian cancer in general population. Hannaford P C and colleagues reported 46% reduction in ovarian cancers among users of oral contraceptives

in a cohort of 1 million women. Chemo-preventive benefits of oral contraceptives have been found to be associated with duration of its use, time since last use and age of first use of the contraceptives. (13) Use of oral contraceptives at an early age confers long-term protection against development of ovarian cancer. (14) Fenretinide (4-HPR) one of the most important promising retinoid is widely studied in chemoprevention trials for breast cancer. It is the synthetic amide of retinoic acid fenretinide, N-4-hydroxyphenyl retinamide (4-HPR). It has been proposed as a preventive agent for high-risk women with BRCA-1 and BRCA-2 mutation carriers with high familial risk. (15) G. de Palo et al studied effect of fenretinide on the occurrence of ovarian cancer in a randomized clinical trial for the prevention of second breast cancer. They observed protective effect of fenretinide against ovarian cancer during 5 year intervention periods, but this effect was not evident after intervention period. (16) Studies demonstrated lower occurrence of ovarian cancer in women exposed to NSAIDs particularly acetaminophen compared to aspirin and ibuprofen through various mechanisms. Controversial observations have been reported about association of NSAIDs with prevention of ovarian cancer. (17) Recently natural compounds like curcumin, epigallocatechin 3-gallate, resvertol, sulforaphane and Withaferin-A have proposed to be safe possible adjuvants along with chemotherapy for secondary prevention in the management of ovarian cancer. They inhibit tumor recurrence through several mechanisms, like inhibition of tumor cell proliferation, stimulation of autophogy and apoptosis and targeting ovarian cancer stem cells. (18) Among BRCA mutant carriers, poly-ribose polymerase inhibitors (PARP) may be possible chemopreventive agents. (19)

Risk-Reducing Bilateral Salpingo-Oophorectomy

Among women with BRCA1 and BRCA2 mutations and Lynch syndrome, prophylactic risk-reducing bilateral salpingo-oophorectomy (rrBSO) after completion of childbearing reduces risk of ovarian cancer by 95%. (4) Also rrBSO protects from breast cancer among high-risk individuals by 30-75%. Relative risk of ovarian cancer after rrBSO reported as 0.04% (95%CI 0.01-0.16). (20) Prophylactic surgical intervention has shown reduced mortality with a hazard ration 0.06 (CI 0.02-0.17) in low risk women and 0.21 (CI 0.12-0.39) among BRCA1/BRCA2 mutant women. (21) But surgical menopause causes vascular instability, hot flushes, osteoporosis, breast and genital tissue atrophy and increases risk of cardiovascular disease. Various study groups like the group of gynecologic oncology suggested cost-effective strategy of risk reduction in post-menopausal women with BRCA mutation. This surgical intervention cannot prevent the development of peritoneal carcinomatosis among high-risk women. (22-24) High-risk women, who have not satisfied parity, cannot opt primary prevention of ovarian cancer by bilateral oophorectomy. Hence other options should be studied for such candidates so as to delay prophylactic surgery. The role of vaccines that stimulate immunity to MUC-1 mucin core protein is controversial for prevention of ovarian cancer in addition to breast cancer.

Conclusion

Ovarian cancer is a devastating fatal disease with limitations of detection at the early stage and effective preventive strategies. The problem with ovarian cancer is availability of very few indicators like family and personal history of cancer or inheritance of mutations in BRCA1 or BRCA2 or other ovarian cancer predisposition genes. Hence, identification of high-risk candidates for chemoprevention of ovarian cancer is the chief concern for implementation of chemoprevention. Development of highly specific and sensitive screening tools for ovarian cancer and implementation of effective preventive strategies is challenging job for the researchers and clinicians. Interventions with targeted therapy are effective among women with BRCA1/ BRCA2 associated tumors.

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Citation: **Dr. Takalkar Unmesh Vidyadhar, Dr. Advani Suresh**. *Prevention of Ovarian Cancer among High-Risk Women. Archives of Oncology and Cancer Therapy. 2018; 1(1): 54-58.*