S15. Ovarian Cancer Prevention + Early Detection: Mission Impossible?

R. Bast

MD Anderson Cancer Center, Unit 355, Houston TX, United States of America

Epithelial ovarian cancer is neither a common nor a rare disease. In the United States, the lifetime risk of ovarian cancer is 1 in 70 and the prevalence in postmenopausal women is 1 in 2500. The prevalence of the disease significantly affects strategies for prevention and detection.

If chemoprevention for ovarian cancer were provided to all women over the age of 50, side effects would have to be minimal in order to achieve an acceptable ratio of benefit to risk. This ratio might be improved by identifying subsets of individuals at increased risk or by "bundling" prevention of ovarian cancer with treatment for other more prevalent conditions. Multiple epidemiologic studies document that use of oral contraceptive agents for as long as 5 years decreases the risk of ovarian cancer in later life by 50%. Approximately 10% of ovarian cancers are familial and relate to mutations of BRCA1, BRCA2 and mismatch repair genes. In one Italian study, fenretinide (4-HPR) delayed development of ovarian cancer in women at increased risk of developing breast and ovarian cancer. Accrual to confirmatory studies has been prohibitively slow and prophylactic oophorectomy is recommended for women at increased genetic risk. More subtle genetic factors are being sought in women with apparently sporadic disease. Vaccines may have a role for prevention of several different cancers. Breast and ovarian cancers express mucins that could serve as targets for preventing both cancers.

Early detection of ovarian cancer requires a strategy with high sensitivity (>75% for stage I disease) and very high specificity (>99.7%) to achieve a positive predictive value of 10% (10 laparotomies for each case of ovarian cancer detected). Transvaginal sonography (TVS) can has achieved these values in some studies, but is limited by the cost of annual screening in a general population. Two stage strategies that incorporate both serum markers and TVS promise to be more cost effective. A rising CA125 has been used to trigger TVS in a small fraction of patients. An algorithm has been developed that calculates risk of ovarian cancer based on serial CA125 values and refers patients at highest risks for TVS. Use of the algorithm is currently being evaluated in a trial with 200,000 women in the United Kingdom that will test critically the ability of a two-stage screening strategy to improve survival in ovarian cancer. Whatever the outcome, as 20% of ovarian cancers have little or no expression of CA125, additional serum markers will be required to detect all patients in an initial phase of screening. More than 30 serum markers have been evaluated alone and in combination with CA125 by different investigators. Some of the most promising include: HE4, mesothelin, M-CSF, osteopontin, kallikrein(s) and soluble EGF receptor. Two proteomic approaches have been used: one examines the pattern of peaks on mass spectroscopy and the other uses proteomic analysis to identify a limited number of critical markers that can be assayed by more conventional methods. Both approaches are promising and require further development. Several groups are placing markers on multiplex platforms to permit simultaneous assay of multiple markers with very small volumes of serum. Mathematical techniques are being developed to analyze combinations of marker levels to improve sensitivity and specificity. In the future, serum markers should improve the sensitivity of detecting recurrent disease as well as facilitate earlier detection of ovarian cancer.