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Short Communication

Precision prevention in ovarian cancer

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Ovarian Cancer (OC) is the most lethal gynecologic malignancy but a timely diagnosis is limited because of the absence of effective biomarkers. Germline *BRCA1*/2 genetic alterations are risk factors for hereditary OC and a Risk-Reducing Salpingo-Oophorectomy (RRSO) is pursued to prevent disease. However, not all healthy carriers develop the disease and RRSO may cause complications such as menopausal symptoms and cardiac risks. In addition, RRSO may not prevent *BRCA1*/2-related primary peritoneal cancer. Therefore, it is necessary to find biomarkers for 'selective' RRSO and chemoprevention strategies against hereditary OC.

Key words: Biomarker, chemoprevention, hereditary ovarian cancer, risk-reducing salpingo-oophorectomy

DESCRITPION

A lack of effective diagnosis and early screening is one of the reasons why Ovarian Cancer (OC) has the highest mortality rate among gynecological malignant tumors. Although Cancer Antigen 125 (CA125) and human epididymis secretary protein 4 (HE4) have been used as markers for the early detection of OC, they lack high sensitivity and specificity (Kristjansdottir et al., 2013). Proteomics is an important technique for discovering biomarkers suitable for the early detection of OC (Hanash et al., 2011). Cancer biomarker discovery, two-dimensional gel electrophoresis, mass spectrometry, and protein microarrays Kolch et al., together with advanced bioinformatics, have become powerful tools for identifying proteins associated with specific cancers (Kolch et al., 2005).

Previous studies showed that germline mutation is a risk factor for hereditary OC (Ramus et al., 2009). Breast Cancer Gene 1 (*BRCA1*) methylation is also associated with the development of hereditary ovarian cancer, especially in those without a cancer status but with family history of cancer (e.g., first - or second-degree relatives of patients with breast, ovarian, or pancreatic cancer) (Jung et al., 2021). Women who have a *BRCA1* or *BRCA2* mutation are at high risk of developing ovarian or breast cancer. Prophylactic surgery can reduce risk by 85% for peritoneal carcinoma and ovarian cancer, and by 90% for breast cancer (Finch et al., 2006; Rebbeck et al., 2004). For healthy women with *BRCA1*/2 germline mutations, a Risk-Reducing Salpingo-Oophorectomy (RRSO) is recommended for the prevention of hereditary OC when child-bearing is completed (Domchek et al., 2010; Daly et al., 2017). However, RRSO may cause early menopausal symptoms (e.g., sweating, insomnia) and also increase osteoporosis and cardiovascular risk (Michelsen et al., 2009). In addition, even after an RRSO, the risk of *BRCA1*/2-related primary peritoneal cancer still remained (Walker et al., 2015). Therefore, novel preventive strategies are necessary in women with a hereditary OC.

For those with hereditary breast cancer, several chemoprevention studies related to receptor activator of nuclear factor kappa-B (RANK)/RANKL (RANK ligand) (Schramek et al., 2010), a key factor in bone metabolism and a vital endogenous factor in raising the risk of breast cancer, are under in progress. RANK/RANKL is known to be associated with mammary gland development during pregnancy, and mammary stem cell expansion and proliferation (Rao et al., 2018). Previous studies reported that RANKL was a potential target for breast cancer prevention in *BRCA1*-mutation carriers and in reducing the time of tumor onset for premenopausal women (Nolan et al., 2016; Sigl et al., 2016).

However, limited studies exist about preventing hereditary OC. Recently, Ahn et al. showed that plasma Secreted Protein and Rich in Cysteine (SPARC) and thrombospondin-1 (THBS1) concentrations in healthy people carrying *BRCA1*/2

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were lower than in OC patients with a *BRCA1*/2 variation (Ahn et al., 2021). The authors suggested that *BRCA1*/2 carriers go through "selective" RRSO only when plasma SPARC or THBS1 concentrations increase by more than 337.35 ng/mL or 65.28 μg/mL, respectively. This study therefore indicates how to reduce the rate of unnecessary oophorectomy, relieve the economic and psychological burden of patients, and avoid waste of medical resources. In addition, the study also showed that an alternative method to RRSO may exist to prevent OC.

Using an animal model, another recent study showed that OC may be prevented by targeting progesterone signaling, especially in OC with deleterious *BRCA1*/2 mutations. The authors used mifepristone, an antiprogestin that is already on the market, in double-knockout (Dicer1–Pten) mice and showed that the treatment profoundly improved mouse survival. The authors suggested that this kind of effective chemopreventive strategy is part of the next-generation precision medicine required to win the "fight against cancer" (Kim et al., 2020).

In summary, women who carry a germline *BRCA1*/2 mutation face a high cumulative breast and ovarian cancer risk. Therefore, chemoprevention (non-surgical prevention) strategies are needed. It is suggested that the highlights of next-generation precision medicine are biomarkers to predict the development of hereditary cancer, and "selective" prophylactic surgery or personalized chemopreventive strategies.

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