The Birth of a New Paradigm--- An Example in Studying Ovarian Cancer Origin

Ie-Ming Shih, MD, PhD
Richard W. TeLinde Distinguished Professor and Director of Women's Malignancy Program
Johns Hopkins University School of Medicine

Unlike other human cancers of which their tissue origins and pathogenesis in initiation and early progression have been well delineated, ovarian cancer is an exception. The long-held view that ovarian cancer develops from its "cognate" site (i.e., the ovary) has been called into question since there is no compelling evidence to demonstrate precancerous lesions in ovarian tissues and surgical excision of ovaries cannot fully protect women from developing ovarian cancer later in life. This puzzle has intrigued researchers and gynecologists for decades and such deficiency in the knowledge where ovarian cancer comes from has considerably compromised the major attempts aiming at reducing its mortality and morbidity through early detection and prevention in women suffering from this devastating disease. As Thomas Kuhn proposed in his book (The Structure of Scientific Revolutions), "when puzzles arise that repeatedly resist solutions a crisis of confidence occurs. During a crisis, the paradigm is subjected to testing and might be rejected. If that occurs, a new paradigm replaces the previous one and a scientific revolution has occurred". In this case, we have witnessed the birth of new paradigm in the cell origin of ovarian cancer which was initiated by the observation about 2 decades ago that dysplastic epithelium was observed in the fallopian tube in women carrying BRCA1 and BRCA2 germline mutations who are genetically predisposed to develop ovarian and breast carcinomas. Subsequent studies in epidemiology, pathology, molecular analysis and animal models provide compelling data to support this new paradigm. The tubal paradigm of ovarian cancer development posits that carcinogenesis takes place in fallopian tube epithelium rather than in ovarian surface epithelium by repeated exposures to reactive oxygen species-enriched follicular fluids. Subsequent DNA damages result in somatic mutations in *TP53* which conspires with other microenvrionmental factors transform fallopian tube epithelial cells into a cancer precursor which further undergoes a series of molecular changes to become frankly malignant and highly invasive ovarian carcinoma. The geographical location of the fallopian tubes which open their lumens directly to the ovary and peritoneal cavity positions the precursor tumor cells to reach not only ovaries to establish ovarian tumors but also to peritoneal wall, omentum and mesentery to form disseminated diseases upon diagnosis. At the same time, the tumor cells derived from tubal precursors can also travel down to uterine cavity then cervix where the rare tumor cells can be sampled by routine Pap smear and analyzed for molecular genetic and epigenetic alterations. Current efforts have been invested to develop a clinical test for early diagnosis of ovarian cancer. The advent of this paradigm should have an impact on our understanding how an ovarian carcinoma arises and provide a model for exploring opportunities for its early detection and prevention.