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The Role of Oral Contraceptive Pills (OCPs) in Chemoprevention of Epithelial Ovarian Cancer in Women with Mutant BRCA1 and BRCA2 Genes

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There are more than 190,000 new cases of ovarian cancer diagnosed every year worldwide. Ovarian cancer is the second most common gynecological cancer and leading cause of death from gynecological cancer in the western hemisphere. Approximately 10% of ovarian cancers may be due to an inherited genetic predisposition. Hereditary ovarian–breast cancer syndrome is associated with mutations in the BRCA1 and BRCA2 genes located on chromosomes 17 and 13, respectively. Women with a BRCA1 mutation have an 85% risk of developing breast cancer, a 60% risk of ovarian cancer by age 70, and an increased risk of colon cancer. Those with mutations of the BRCA2 gene have a lower cancer risk. Epithelial ovarian adenocarcinomas that occur in a hereditary setting due to transmitted germ-line BRCA1 mutations are predominantly of the serious type, with representation of mucinous and border line tumors. Estrogen alpha & beta subtypes, and progesterone subtypes 1&2 have 3 effects: variable expression of Estrogen and progesterone subtypes at the effector tissues level, receptor subtype change related to the specific ligand, and binding to the co-regulator proteins receptors. The relation between these 3 effects accounts for the molecular effect of selective estrogen receptor modulator (SERMs), estrogen and progesterone. It is known that, infertility and low parity contribute to increased risk of sporadic ovarian cancer. The effective screening for epithelial ovarian cancer in the general population has not been established. Females with BRCA1 and BRCA2 mutations require different approach to evaluate their risk status. Bi-annual measurements of CA125 and transvaginal sonography have not been shown to increase patient's survival, however it is recommended in high risk patients. The preferred method to prevent the hereditary–ovarian breast cancer syndrome, in high-risk patients, is to perform a prophylactic oophorectomy using assisted video-laparoscopy, or robot-assisted laparoscopic surgery [1]. The apoptic characteristics of BRCA1 gene therapy may have the potential to prevent the progression of ovarian cancer, and enzyme/prodrug gene therapy could be an efficient approach to do so [2]. BRCA1 and BRCA2 are the two major susceptibility genes involved in hereditary breast and ovarian cancer. BRCA1 and BRCA2 mutation carriers have a 54–85% and 45%. Lifetime risk of developing breast cancer, respectively, and an 18–60% and 11–27% lifetime risk of developing ovarian cancer, respectively [3]. BRCA1 mutation carriers have also a risk for fallopian tube carcinoma [4], and primary peritoneal carcinoma [5]. In a study [6], which identified women with BRCA1 and 2 mutations from an international registry between 1992 and 2003, found that bilateral salpingo-oophrectomy (BSO) was associated with decreased risk of ovarian cancer and fallopian tube cancers. The authors noted that the estimated cumulative incidence of peritoneal cancer was 4.3%, 20 years following BSO. , and the adjusted reduction in ovarian cancer risk associated with BSO was 80%. It is noteworthy, that women who carry BRCA mutations are diagnosed with epithelial ovarian cancer at an earlier age than women who do not have the mutations [30]. Narod et al. [7] noted that OCPs usage may reduce the risk of epithelial ovarian cancer in women with mutants BRCA1 and 2 genes. My view is that, premenopausal women with BRCA1 and 2 genes mutations should use continually OCPs, but they should be aware that may slightly increase their risk of having breast cancer. There is compelling evidence that OCPs can reduce the risk of ovarian cancer in general population [8-11]. A cohort study using data of over 1 million women-years of observation reported that ever OCPs use was associated with a 46% reduced risk of ovarian cancer compared with never use [9]. The reduced risk was related to the duration of use, with a significant decrease among women using the pill for more than 8 years, and the protective effect persisted 15 years after stopping the use. It has been shown that the risk of ovarian cancer had decreased in women who discontinued OCPs after usage for 30 years or longer [10]. Low dose estrogen oral contraceptives confer substantial protection against ovarian cancer [12-16]. A population-based case–control study showed no significant difference in ovarian cancer risk between women who took low-dose estrogen pills (<50 μg ethinyl estradiol or <80 μg mestranol) and those who received higher-dose estrogen pills [13]. Another study reported that, per each year of use of pills containing <35 μg, 35 to <50 μg and >50 μg ethinyl estradiol, the odds ratio [OR] s were 0.86 (95% CI = 0.77–0.94), 0.91 (95% CI = 0.83–1.00) and 0.95 (95% CI = 0.91–0.99) [14]. OCPs with high-potency progestin seemed to be more protective against ovarian cancer than those with low-potency progestin [15]. Rodriguez et al. [16,17] randomized female macaques to receive a diet containing no hormones, ethinyl-estradiol, levonorgestrel or ethinyl-estradiol plus levonorgestrel., the ovaries from progestin- treated animals showed a decrease in the expression of transforming growth factor [TGF]-β1 and an increase in the expression of TGF-β2/3. The apoptotic index of the ovarian epithelium was related to the changes in expression of TGF-β isoforms induced by progestin treatment. The exposure of immortalized normal and malignant human ovarian surface epithelial cells to progesterone has been found to enhance the expression of Fas ligand (FasL) and to induce activation of caspase-8 and caspase-3 [18]. It has been shown that estrogen may enhance cell proliferation [19,20] and prevent apoptosis through up-regulation of the anti-apoptotic Bcl-2 gene in ovarian epithelial cells [21]. It was observed that OCPs use may reduce ovarian cancer risk in BRCA mutation carriers [7,22-25]. A case–control study of the

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Hereditary Ovarian Cancer Clinical Study Group [23] showed that OCPs use reduced ovarian cancer risk in both BRCA1 mutation carriers and BRCA2 mutation carriers. The risk reduction was higher with increasing duration of use.

Antonoiu et al. [25] assessed BRCA1 mutation carriers and BRCA2 mutation carriers from the International BRCA1/2 Carrier Cohort Study to evaluate the effect of reproductive and hormonal factors on ovarian cancer risk. They observed that BRCA1 carriers who had ever taken pill had a reduced risk of developing ovarian cancer and increasing duration of use was associated with a significantly reduced risk ($p = 0.0004$). A case–control study including 1311 pairs of women with BRCA mutations, showed that ever pill use was associated with an increased risk of breast cancer among BRCA1 mutation carriers (OR = 1.20; 95% CI = 1.02–1.40) but not among BRCA2 mutation carriers (OR = 0.94; 95% CI = 0.72–1.24) [26]. It was shown in hen, as an animal experimental model, that treatment with progestin alone and in combination with estrogen decreased the prevalence of ovarian cancer. A significant risk reduction of 91% was observed in the group treated with progestin alone (risk ratio = 0.0909; 95% CI: 0.0117-0.704) and an 81% reduction was observed in the group treated with progestin plus estrogen (risk ratio = 0.1916; 95% CI = 0.043-0.864). Egg production was also significantly reduced in these treatment groups compared with control [27]. Iodice et al. [28], performed meta-analysis on the association between OCP use and breast / ovarian cancer in BRCA1/2-mutation carriers. They noted, OCPs use at any point during one's life was associated with a 50% relative risk reduction in developing ovarian cancer for BRCA1/2-mutation carriers. Each 10-year period of OCP use resulted in a 36% relative risk reduction for the development of ovarian cancer. In this meta- analysis, there was no evidence of a significant association between OCP use and breast cancer risk. OCPs formulations used before 1975 correlated with an increased risk of breast cancer, but there was no correlation with the use of more recent formulations [29].

It was noted in, In 33 out of 45 epidemiological studies including 17 099 out of 23 257 cases that ovarian cancer risk declined by 21% for each 5 years of hormonal contraception use, which is similar to the 20% observed in all women, thus indicating that the results were representative of the whole women population [30]. The ovarian cancer relative risk (RR) seems to decrease by 20% for each 5 years of use and for women who had taken oral. Contraceptives for more than 15 years the risk for ovarian cancer is almost halved and decreasing with further use. A minimum period of 1-year use is necessary to obtain the protective effect. It seems that a significant protective effect remains a long time after ceasing OCP's. The protective effect seems to be independent from the type of oral contraceptives formulation. Due to the protective effect of oral contraceptives, It is recommended that women at increased risk of ovarian cancer to use oral contraceptive pills for 5-7 years early in life (<21 years of age), when the incidence of breast cancer is low, and the advantage would be risk reduction of ovarian cancer for life. Patients with hereditary breast and ovarian cancer disease are unique, because of age of diagnosis, pathological features, and prognosis. In BRCA1/2 mutation carriers, the surgical prophylactic procedure includes peritoneal lavage and cytological examination to detect occult ovarian, peritoneal or tubal cancers, and bilateral salpingo-oophorectomy. Occult ovarian, peritoneal or tubal cancers, are reported to be present in about 3% of BRCA1/2 carriers who undergo prophylactic bilateral salpingo-oophrectomy (pBSO). Ovaries and tubes should be handled with care not to spread occult cancer through the abdominal cavity. Ovaries and tubes should be removed using an endo-pouch. In addition, during the histopathological examination, it is important that the entire ovaries and fallopian tubes are serially sectioned so that small and microscopic lesions are not missed [31]. BRCA1/2- mutation carriers should be offered risk reduction strategies, in the form of minimally invasive. Prophylactic bilateral mastectomy and/or robot- assisted laparoscopic- bilateral salpingo-oophorectomy a by age 40 years, or when childbearing is complete. OCPs may be used effectively to reduce the risk of ovarian cancer.

There are indications that targeted therapy is effective in women with BRCA1/BRCA2-associated tumors. Recent studies have indicated that tumors with BRCA mutations, are sensitive to polyp-ribose polymerase inhibitors (PARP inhibitors) [32]. Initial trials show good efficacy and tolerability for PARP inhibitors) in mutation carriers with advanced ovarian cancers. These agents might also potentially be used in chemoprevention.

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