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Review article

Narrative

Chemoprevention for ovarian cancer

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ABSTRACT

The ovarian cancer represents the main gynecologic cancer mortality in the world, and the epithelial neoplasms are the most frequent. The antineoplastics have contributed little to the survivor in these patients, also screening has not been shown to reduce mortality. Patients who have genetic disorders such as BRCA 1 and 2, Lynch syndrome have predisposition to developing ovarian cancer, so in these cases should be performed bilateral salpingo-oophorectomy. It is the best prophylactic option. The Oral contraceptives are a primary prevention strategy for ovarian cancer patients, especially those who doesn´t have satisfied parity. A meta-analysis showed that the use of oral contraceptives at an early age is a protective factor for ovarian cancer, which has maintained over the next 20 years after his suspension.

Key words: *Ovarian cancer, chemoprevention, combined oral contraceptive.*

RESUMEN

El cáncer de ovario representa la neoplasia con mayor mortalidad en el mundo, la neoplasia epitelial es la más frecuente entre ellos. Los tratamientos antineoplásicos han contribuido poco en incrementar la sobrevida de los pacientes; sin embargo, el tamizaje no ha disminuido la mortalidad. Pacientes con trastornos genéticos hereditarios como BRCA1 y 2, síndrome de Lynch tienen predisposición de presentar cáncer de ovario, por lo que la salpingooforectomía bilateral es una alternativa preventiva. Los anticonceptivos orales combinados son una alternativa de prevención para cáncer de ovario, especialmente en aquéllos que aún no completan paridad, los meta-análisis demuestran que el uso de anticonceptivos orales en edad temprana generan protección hasta por 20 años posterior a suspenderlos.

Palabras clave: *Cáncer de ovario, quimioprevención, anticonceptivos orales combinados.*

INTRODUCTION

Among gynecologic malignancies, ovarian cancer represents the highest mortality.[1] In the United States, 22,280 new cases of ovarian cancer are diagnosed and 14,240 deaths *(Figures 1 and 2)*.[2] Epithelial neoplasia are the most frequent histological subtypes that include: serous, mucinous, endometrioid, clear cell, undifferentiated and not typified.[3] These subtypes have different genetic characteristics and molecular patogenesis that is demonstrated due to varied susceptibility between citotoxic chemotherapies.[4,5]

Advances in cancer treatments have only been able to increase survival in a few cases in the last 20 years, is still regarded as the neoplasia with the highest mortality among gynecologic cancers.[6] The screening has not shown to reduce mortality and has not been established as a measure of primary prevention,[7] the surgical removal of both ovaries and oviducts is only prophylactic intervention that has shown reduced mortality with a hazard ratio (HR) 0.06 (CI 0.02 to 0.17) in low-risk population[8] and 0.21 (CI 0.12 to 0.39) in patients BRCA1/BRCA2 mutated.[9] Patients with Lynch syndrome mutations (mutations MLH1 and MSH2) has a risk of 20% (CI 1-65%) and 24% (CI 3-52%) respectively.[10] However this method has been only established for populations at higher risk (risk for ovarian cancer survival > 10%) and female carriers with high penetrance of BRCA1/BRCA2 or MMR (mismatch repair gene mutations), where the cost-benefit is well established.[11]

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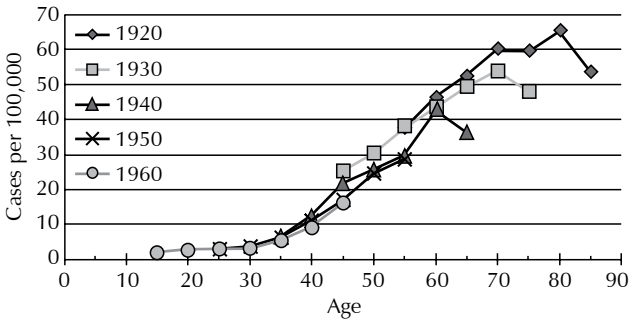

Figure 1. *Incidence by age group, obtained from the National Cancer Institute's SEER registry surveillance, epidemiology, and end results.*

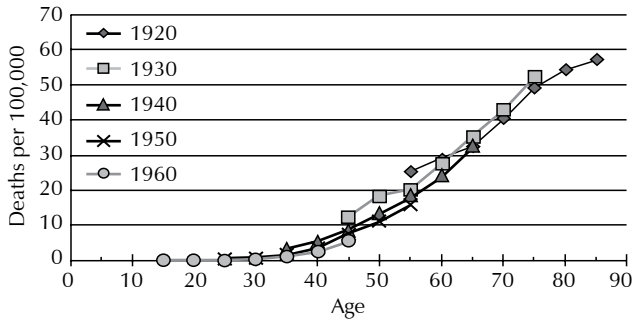

Figure 2. *Specific mortality by age group, obtained from the National Cancer Institute's SEER registry surveillance, epidemiology, and end results.*

In the general population (low risk), the global distribution of ovarian cancer includes women with an estimated lifetime risk very low (1.3-2%) and moderate (less than 10%).[12] Lifestyle, reproductive history, medical history, use of oral contraceptives, tubal sterilization, parity, endometriosis, infertility, age, family history and genomic variants are risk factors associated with ovarian cancer;[13] although individual risk is very variant, women with multiple risk alleles are 2-3 times more at risk than those estimated polygenic low load.[14]

PRIMARY PREVENTION

Because the effectiveness of screening for reducing morbidity and mortality is limited due to the biology of the disease, alternative strategies should be implemented, including primary treatment with less toxicity if the disease is already diagnosed.

PROPHYLACTIC SURGERY

The bilateral salpingo-oophorectomy is a procedure for primary ovarian cancer prevention; is an established measure for high-risk patients that has shown to reduce ovarian, peritoneum and fallopian tubes cancer up to 80% and a reduction in breast cancer of 50%.[15] Various study groups, including the group of gynecologic oncology (SGO), have implemented prophylactic surgery as health economic model demonstrating cost-effective risk reduction in population with BRCA mutation.[16] Because of the risks of prophylactic surgery and premature loss of ovarian function, this is not recommended in premenopausal patients with no other indication of pelvic surgery; There is evidence from observational studies, where gynecological procedures performed for other indications (tubal ligation and hysterectomy) also reduce the risk of cancer, including procedures that not merited resection of the ovaries.[17-19] There is evidence that resection of fallopian tubes for tubal sterilization or during a hysterectomy without oophorectomy for other gynecological indications, confers protection against ovarian cancer.[20]

ORAL CONTRACEPTIVES

Oral contraceptives are a primary prevention strategy for ovarian cancer, multiple studies have demonstrated a risk reduction of up to 50% with long-term use, preventing up to 200,000 cases and 100,000 deaths from the disease.[21]

In women at high risk of developing ovarian cancer, either by family history or known mutation, the effect of oral contraceptives is important for many reasons. First, the incomplete penetrance of hereditary cancer genes suggests that in addition to these there are other factors (eg, environmental factors) that influence the development of cancer in carriers and noncarriers women, and so from the etiological point of view, understanding the influence of prolonged exposure to oral contraceptives and development or ovarian cancer. Second, women with high genetic risk must understand the different prophylactic options that reduce morbidity and/or mortality from ovarian cancer, including prophylactic surgery; so far screening in high-risk patients is not an option accepted with statistical impact.[22-24] chemoprevention is an option to reduce the risk of ovarian cancer, particularly in high-risk women who have not yet satisfied parity and they want to delay prophylactic surgery.

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EVIDENCE OF THE CHEMOPREVENTIVE BENEFIT OF ORAL CONTRACEPTIVES

Duration of contraceptive use

A meta-analysis which included seventeen studies,[25-40] analyzed the relationship between duration and prevention between the use of oral contraceptives and frequency of ovarian cancer. Women who use birth control the first twelve months showed no protection against ovarian cancer, compared with those who used more than 10 years, this being the group with the most benefit *(Table 1)*.[41]

Age of first use of the contraceptive method

Seven studies[25,29,32,36,37,41,42] were included in a meta-analysis which assesses the age of onset of contraceptive use and the risk of developing ovarian cancer, for which 3,552 cases were included and 4,713 controls. They achieved to demonstrate an inverse relationship between contraceptive use and the incidence of ovarian cancer, so patients who began oral contraceptive use before age 20 had a lower risk of ovarian cancer; while older starting at > 30 years show less or no protection against cancer. With this we conclude that the use of oral contraceptives at an early age is a protective ovarian cancer long-term factor *(Table 2)*.[42]

Table 1. Time results on the use of oral contraceptives and ovarian cancer prevention.[41]

Duration (months)	Odds ratio (95% CI)	p-value
1-12	0.91 (0.78 to 1.07)	0.2504
13-60	0.77 (0.66 to 0.89)	0.0014
61-120	0.65 (0.55 to 0.77)	< 0.0001
> 120	0.43 (0.37 to 0.51)	< 0.0001

Table 2. Risk of ovarian cancer by the age of onset of contraceptive use.[41]

Age of onset (years)	Odds ratio (95% CI)	p-value
< 20	0.63 (0.45 to 0.89)	0.018
20-24	0.71 (0.51 to 0.99)	0.044
25-30	0.67 (0.46 to 0.99)	0.045
> 30	0.89 (0.60 to 1.32)	0.489

Table 3. Incidence of ovarian cancer by the time of suspension of contraceptive treatment.[41]

Age (years)	Odds ratio (95% CI)	p-value
0-10	0.41 (0.34 to 0.50)	< 0.0001
10-20	0.65 (0.56 to 0.74)	< 0.0001
20-30	0.92 (0.76 to 1.12)	0.3692
> 30	0.79 (0.58 to 1.12)	0.1036

Time since last use of oral contraceptives

A meta-analysis that presents[24,27,28,32-34,36,39,42] nine studies in which they compared the time of suspension of contraceptives and the risk for developing ovarian cancer, showed that the protective effect of oral contraceptives is present up to 20 years after suspension, after this time a loss occurs in the protection as the years pass until they pass more than 30 years from the suspension, where the risk is the same than to the general population and the benefit of use of oral contraceptives is lost *(Table 3)*.[41]

CONCLUSIONS

The use of oral contraceptives and even injections or patches has shown a significant reduction in risk of epithelial ovarian cancer, this benefit is permanently up to 20 years later. Its use should be recommended in units of primary health care, use of these methods as family planning and protection from ovarian neoplasias, among others. Long duration methods such as subdermal implants and intrauterine hormonal systems also have the benefits of risk reduction.

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