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SPECIAL ARTICLE

Genetic counseling, testing and management of epithelial ovarian carcinoma patients: recommendations from a consensus of experts from the National Institute of Neoplastic Diseases of Peru

Asesoramiento genético, testeo y manejo de pacientes con carcinoma epitelial de ovario: recomendaciones de un consenso de expertos del Instituto Nacional de Enfermedades Neoplásicas del Perú

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ABSTRACT

The objective was to provide tools for the profiling and management of patients with epithelial ovarian cancer through genetic testing. The Consensus was made up of experts in oncology and genetics from the National Institute of Neoplastic Diseases of Peru and followed the guidelines of the Consensus Conference on Standard Operating Procedures of the European Society of Medical Oncology. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used to assess the evidence and make recommendations. The clinical practice guidelines were graded following the Appraisal of Guidelines for Research and Evaluation instrument II (AGREE II). Genetic counseling and testing is recommended for all patients with epithelial ovarian cancer. Regardless of the findings in the tumor, germinal testing should be performed. Testing is suggested to include *BRCA1, BRCA2, ATM, BRIP1, MLH1, MSH2, MSH6, PALB2, RAD51C, RAD51D, TP53, PTEN, PMS2, EPCAM* and *NBN*. Test findings can guide pharmacological treatment. In conclusion, patients with epithelial ovarian cancer and their relatives at risk should be identified and provided with genetic counseling. The recommendations given in this consensus will be useful if they are known and implemented. Genetic counseling and testing are expected to be included in daily clinical practice.

Keywords

Carcinoma, ovarian epithelial; Genetic counseling; Genetic profile; Consensus; Poly(ADP-ribose) polymerase inhibitors (source: MeSH NLM).

RESUMEN

El objetivo fue proporcionar herramientas para el perfilamiento y manejo de pacientes con cáncer epitelial de ovario mediante pruebas genéticas. El Consenso estuvo conformado por un grupo multidisciplinario y balanceado de médicos especialistas expertos en oncología y genética pertenecientes al Instituto Nacional de Enfermedades Neoplásicas y se realizó siguiendo los lineamientos de la "Conferencia de consenso de procedimientos operativos estandarizados de la sociedad Europea de Oncología Médica. La aproximación de calificación de recomendaciones, su desarrollo y evaluación (GRADE) se utilizó para evaluar la evidencia y hacer recomendaciones. Las guías de práctica clínica fueron calificadas por dos evaluadores siguiendo el "Instrumento para la apreciación y la evaluación de guías de práctica clínica II (AGREE II). A toda paciente con cáncer epitelial de ovario a quien se le recomiende una evaluación genética, debe ser asesorado genéticamente. Para todas las pacientes con cáncer epitelial de ovario, se recomienda testeo germinal. Por otra parte, el testeo somático puede proporcionar información que sugiera un potencial hallazgo germinal. Se sugiere que a toda paciente con cáncer epitelial de ovario no mucinoso se le realice testeo genético que incluya *BRCA1, BRCA2, ATM, BRIP1, MLH1, MSH2, MSH6, PALB2, RAD51C, RAD51D, TP53, PTEN, PMS2, EPCAM* y *NBN*. El resultado del testeo genético puede guiar el tratamiento farmacológico. En conclusión, las pacientes con cáncer epitelial de ovario y sus familiares deben de ser identificados y deben de recibir el asesoramiento genético correspondiente. Las recomendaciones de esto consenso se consideran de utilidad y deberían ser implementadas. El asesoramiento genético y el testeo deben ser incluidas en la práctica clínica del día a día.

Palabras clave

Carcinoma epitelial de ovario; Asesoramiento genético; Perfil genético; Consenso; Inhibidores de poli(ADP-ribosa) polimerasas (fuente: DeCS BIREME).

INTRODUCTION

Cancer is a type of genetic disease in which not one, but many mutations are required [1]; however, not all these mutations are inherited in families. For example, sporadic mutations occur in tumor/somatic cells only. On the other hand, genetic cancer predisposition syndromes are often characterized by variants associated with an increased risk for certain cancers (i.e., a high penetrance phenotype) and transmission to offspring through the mother and/or father [2]. Scientific and technological advances in genomics are revolutionizing our approach to genetic counseling, genetic testing, and target therapies, fulfilling the promise of personalized medicine [3].

The incidence rate of ovarian cancer in Peru was 6.7 cases per 100,000 inhabitants per year and the standardized adjusted mortality rate was 4.0 per 100,000 inhabitants according to data from Globocan 2020 (Global Cancer Observatory) [4]. Between 85%-90% of all ovarian cancers are epithelial in origin, and approximately 70% of all epithelial ovarian cancers are high-grade serous adenocarcinoma (HGS) [5]. Approximately 25% of all ovarian cancers are caused by genetic conditions. Of these, mutations in the *BRCA*1 and *BRCA*2 genes occur in approximately 18% of epithelial ovarian cancers and approximately 6% of these are caused by genes other than *BRCA*1 and *BRCA*2, including homologous recombination-associated genes (HRR) [6].

The cumulative ovarian cancer risk for *BRCA*1 mutation carriers is approximately 40% and 18% for *BRCA*2 [7]. Approximately 41%-50% of epithelial ovarian cancers exhibit homologous recombination deficiency (HRD) [8] involved in DNA damage repair and replication.

The main clinical practice guidelines (CPG) in the world recommend the use of poly (ADP)-ribose polymerase

inhibitors (PARPi) as maintenance treatment in these patients with advanced disease after first line and at recurrence [9-12].

Medical societies recommend genetic testing for all women diagnosed with ovarian cancer, but only 30% of women undergo genetic testing [13]. Additionally, there is still a lack of resources and strategies on how to best incorporate genetic testing into medical practice.

This consensus aims at providing recommendations and tools for the profiling of patients with epithelial ovarian cancer and seeks to impact prevention, early detection and treatment with targeted therapies. It is important to sensitize the medical staff in the identification and suspicion of genetic alterations in these patients, to reduce clinical variability in treatment and to optimize timely referral to a geneticist. The recommendations given in this consensus are not a substitute for medical judgment, they are only a support for decision making.

METHODS

The Consensus was formed by specialists in oncology and genetics (6 clinical oncologists and 1 geneticist) who work at the National Institute of Neoplastic Diseases (INEN) and was carried out following the guidelines of the "Consensus Conference on Standard Operating Procedures of the European Society of Medical Oncology (ESMO) [14].

In a first virtual meeting with the panel, the questions to be answered in the consensus were drafted and voted on. The definition of the clinical questions took into account the existence of controversy in the management or lack of clear guidelines and valid evidence of the efficacy of interventions. A total of 5 questions were defined. There was total agreement. 7/7 (100%) of the votes agreed with each of the questions.

The outcomes of questions 1, 2, 3, 5 were considered critical and the outcomes of question 4 were considered important but not critical.

A systematic search of the literature was carried out to identify the clinical practice guidelines (CPG) and to evaluate the relevance of adopting or adapting some of their recommendations. Databases consulted: PubMedD/MEDLINE (Public Medical Literature Analysis and Retrieval System Online). Limits: Clinical practice guidelines, published in Spanish or English, in the last 10 years. The search was supplemented in the Guidelines International Network (GIN) database.

Strategy of the search: (("ovarian neoplasms"[mh] OR (("ovarian"[tw] OR "ovary"[tw]) AND ("neoplasm*"[tw] OR "cancer"[tw] OR "carcinoma"[tw]))) AND ("genes, brca1"[mh] OR "BRCA1"[tw] OR "BRCA-2" [tw] OR "genes, brca2"[mh] OR "BRCA2"[tw] OR "BRCA-2"[tw] OR "BRIP1"[tw] OR "BRIP-1"[tw] OR "PALB2"[tw] OR "PALB-2"[tw] OR "BARD1"[tw] OR "BARD-1"[tw] OR "RAD51C"[tw] OR "RAD51D"[tw] OR "SMARCA4"[tw] OR "ARID1A"[tw] OR "CCNE1"[tw] OR "CCNE-1"[tw] OR "WT1"[tw] OR "WT-1"[tw] OR "BRAF"[tw] OR "PIK3CA"[tw] OR "PTEN"[tw] OR "ATM"[tw] OR "TP53"[tw] OR "TP-53"[tw] OR "MLH1"[tw] OR "MLH-1"[tw] OR "MSH2"[tw] OR "MSH-2"[tw] OR "MSH6"[tw] OR "MSH-6"[tw] OR "PMS2"[tw] OR "PMS-2"[tw] OR "CDK12"[tw] OR "CDK-12"[tw] OR "receptor, erbb-2"[MH] OR "ERBB2"[tw] OR "ERBB-2"[tw] OR "EPCAM"[tw] OR "KRAS"[tw])) Filters: Practice Guideline, English, Spanish, from 2011/1/1- 2021/12/31

The systematic search for epithelial ovarian cancer yielded a total of 13,466 references, 7,844 published in the last 10 years in any language. Filtering by clinical practice guidelines, articles in Spanish or English, yielded 22 results for full-text review. These searches were extended to GIN, a site that compiles CPGs. Fourteen CPGs were identified that met the selection criteria for review and evaluation. The searches were conducted by a bioinformatics expert. Search update date: January 2022.

The CPGs were scored by two raters following the Assessment of Guidelines for Research and Evaluation Instrument II (AGREE II) [15]. Most of the evaluated guidelines could be recommended (n=9) or recommended with modifications (n=5) for use in clinical practice. The overall evaluation score of the guidelines was between 100% and 80% (for 9 guidelines), between 79 - 60% (for 3 guidelines) and between 50% and 59% (for 2 guidelines). (Details about the evaluation of the selected CPGs in the Supplementary Appendix available at onkoresearch.com).

All the questions posed are answered in more than one of the CPGs reviewed. Therefore, no *de novo* searches were performed. The CPGs that cover the questions of interest meet the desired thoroughness. The recommendations given by the CPGs and answering each of the consensus questions were put to the panel for consideration and voting.

The titles and abstracts of the searches were reviewed by two reviewers who applied the selection criteria defined for each question independently. Once the selection was completed, it was compared for disagreement. The generic inclusion criteria taken into account were: Include the target population, the intervention and the comparator of interest for each question. And the following exclusion criteria: To be written in a language other than English or Spanish.

For each question, a protocol was prepared that included: the search strategy and results, a brief review of the literature identified and its methodological quality, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [16] summary of findings table to support the panel in formulating recommendations.

The quality of evidence, also referred to as confidence, reflects the degree of confidence we have that the estimate of an effect is adequate to support a recommendation. Although the quality of evidence is a continuous spectrum, GRADE [17] proposes a classification into four categories (high, moderate, low and very low). (Details about of quality of evidence in the Supplementary Appendix, available at onkoresearch.com).

The GRADE [17] methodology was also used to grade the strength and direction of the recommendations. Based on the judgment obtained on each of the aspects presented and the balance between risks and benefits, the panel formulated the recommendations according to the criteria proposed by the GRADE. (Details about GRADE can be found in the Supplementary Appendix, available at onkoresearch.com).

To generate the recommendations, two virtual meetings of four hours each were held via the Zoom® platform. The meetings were led by a methodological expert. All panel members received the information to be discussed prior to each meeting. The methodological group presented the evidence in summary. An open discussion was held with the participation of all attendees. After drafting and adjusting the recommendation, it was put to a vote through the Google forms® electronic voting system, which keeps the vote anonymous. The margin for accepting the recommendation after discussion was established as a vote of ≥ 80% of the total number of persons eligible to vote on each of the questions (Table 1).

Subsequently, a draft of the final consensus document was generated, incorporating adjustments according to the additional contributions of the panelists, socialized and submitted for peer review. The meetings were audio and video recorded for later reference.

Update of the Consensus:

This consensus will be updated every three years from its publication date in the event of new evidence that sways in or against the direction of any of the recommendations.

Table 1. Level of agreement by voting on consensus recommendations.

Question and Recommendation	Level of panel agreement	
	(%)	n/N
What profile of a patient with epithelial ovarian cancer would be suitable for genetic counseling? Genetic counseling is recommended for any patient with epithelial ovarian cancer who is ordered to undergo genetic testing.	85.7	6/7
Which criteria must a patient with epithelial ovarian cancer meet for a genetic testing to be indicated? It is recommended that all patients with non-mucinous epithelial ovarian cancer undergo genetic testing.	100	7/7
What are the genes to be evaluated in patients with epithelial ovarian cancer? It is suggested that all patients with non-mucinous epithelial ovarian cancer undergo genetic testing that includes the genes (*BRCA1, BRCA2, ATM, BRIP1, MLH1, MSH2, MSH6, PALB2, RAD51C, RAD51D, TP53, PTEN, PMS2, EPCAM, NBN*). In any case, it is suggested that the type of genes contained in the genetic testing panel should depend on the best available evidence at the time of sampling.	100	7/7
What recommendations do clinical practice guidelines give about somatic testing in patients with epithelial ovarian cancer? Regardless of the findings in the tumor, germline testing should be performed if clinically indicated (and for epithelial ovarian cancer, testing is clinically indicated), and tumor testing may provide information suggestive of a potential germline finding. Pathogenic or probably pathogenic variables reported in the tumor may be of somatic or germline origin	85.7	6/7
What is the multidisciplinary team's recommendation for the therapeutic (pharmacological) management of patients with epithelial ovarian cancer who are negative, positive or inconclusive for a variant of unknown significance (VUS) for the BRCA1/2 genes of the homologous recombination repair (HRR) pathway at either the somatic or germline level? For positive, negative or unknown results, see Table N°4. VUS result: Clinical decisions should not be based on a VUS result. Reclassification of the VUS result is an ongoing process and eventually it is possible to determine definitively whether the variant is deleterious or benign. Until that time, the patient's clinical features and family history should guide clinical decision making.	100	7/7

If there is no new evidence, it will be reviewed again in three years.

In the event of new evidence that modifies any of the recommendations of the consensus, it will be updated every three years after its publication. If there is no new evidence, it will be reviewed every three years.

Recommendations

Question 1. *What profile of patient with epithelial ovarian cancer would be suitable for genetic counseling?*

Recommendation: Genetic counseling is recommended for all patients with epithelial ovarian cancer who are ordered to undergo genetic testing. Strong recommendation in favor. Moderate certainty of evidence. Seven CPGs support this recommendation [9,10,18-22].

Good Practice Point: The decision to offer genetic counseling/testing involves three steps: 1) Pretest genetic counseling. 2) Consideration of the most appropriate test. 3) Post-test genetic counseling, when the result is given to the patient [6]. A medical geneticist, oncologist or surgeon with experience and expertise in cancer genetics should be involved in each step of the process. Counseling/testing should be considered when it is likely to impact the risk management and/or treatment of the patient and/or family members who are at risk.

Question 2. *Which criteria must a patient with epithelial ovarian cancer meet for a genetic testing to be indicated?*

Recommendation: It is recommended that all patients with non-mucinous epithelial ovarian cancer undergo genetic testing. Strong recommendation in favor. Moderate certainty of evidence. Nine GPC support this recommendation [9-11,18-23].

Good practice point: All women diagnosed with non-mucinous epithelial ovarian cancer should be offered germline genetic testing for *BRCA*1/2 and other ovarian cancer susceptibility genes, regardless of clinical features of the disease or family history of cancer (strong recommendation in favor). First- and second-degree blood relatives of an ovarian cancer patient with a germline pathogenic or probably pathogenic variant in a cancer susceptibility gene should be offered individualized genetic risk assessment, counseling, and genetic testing (strong recommendation in favor).

Question 3. *What are the genes to be evaluated in patients with epithelial ovarian cancer?*

Recommendation: It is suggested that all patients with non-mucinous epithelial ovarian cancer undergo genetic testing that includes the genes BRCA1, BRCA2, ATM, BRIP1, MLH1, MSH2 MSH6, PALB2, RAD51C, RAD51D, TP53, PTEN, PMS2 ,EPCAM and NBN (Details about risk and definition in the Supplementary Appendix, available at onkoresearch.com). In any case, it is suggested that the type of genes contained in the genetic testing panel should depend on the best available evidence at the time of sampling. Conditional (weak) recommendation in favor. Moderate certainty of evidence, five CPGs support this recommendation [9-11,18,21].

Question 4. *What recommendations do clinical practice guidelines give about somatic testing in patients with epithelial ovarian cancer?*

Recommendation: Regardless of the findings in the tumor, germline testing should be performed if clinically indicated (and for epithelial ovarian cancer, testing is clinically indicated), and tumor testing may provide information suggestive of a potential germline finding. Pathogenic or probably pathogenic variables reported in the tumor may be of somatic or germline origin. Conditional (weak) recommendation in favor. Low certainty of evidence. Three CPGs support this recommendation [9,18,21].

Question 5. *What is the multidisciplinary team's recommendation for the therapeutic (pharmacological) management of patients with epithelial ovarian cancer who are negative, positive or inconclusive for a variant of unknown significance (VUS) for the BRCA1/2 genes of the homologous recombination repair (HRR) pathway at either the somatic or germline level?*

Recommendation: For positive, negative or unknown results, see more in the Supplementary Appendix, available at onkoresearch.com

VUS result: Clinical decisions should not be based on a VUS result. Reclassification of the VUS result is an ongoing process and it is possible to eventually determine definitively whether the variant is deleterious or benign. Until that time, the patient's clinical features and family history should guide clinical decision making. Strong recommendation in favor. Certainty of evidence is high. Eight CPGs support this recommendation [9,11,12,21,24-27].

DISCUSSION AND CONCLUSIONS

Genetic risk assessment for epithelial ovarian cancer is a multistage process that involves identifying and counseling individuals at risk for familial or hereditary cancer. Its purpose is to educate individuals on genetic, biological and environmental factors related to cancer diagnosis and/or risk. Testing should be considered in patients with a personal or family history suggestive of genetic susceptibility and for whom the result will help with risk management and treatment.

Genetic testing strategies are greatly facilitated when a pathogenic or probably pathogenic variant has already been identified in a family member. In such a case genetic testing can be limited to searching for pathogenic or probably pathogenic variants in other family members at the same location in the gene. However, if there is reason to suspect more than one pathogenic or probably pathogenic variant in the family, then more extensive testing should be considered. Upon the finding of a variant of unknown significance (VUS), a genetic alteration that may at the time represent a benign polymorphism unrelated to an increased risk of cancer or may indicate an increased risk of cancer, the patient should be considered for inclusion in a clinical trial that allows the variant to be followed over time. Advances in sequencing technologies have resulted in the increasing availability of multigene panels for genetic analysis. Given the small number of patients carrying some of these mutations, the level of evidence is basically expert opinion. A disadvantage of multigene panels is that they are most often reporting VUS.

Performing germline or tumor testing sequentially or in combination will depend on national health regulations and existing guidelines for each country. In any case, the identification of deleterious *BRCA*1 and *BRCA*2 mutations in tumor tissue requires subsequent germline testing to assess the heritability of such variation after appropriate genetic counseling. Patients with ovarian cancer without deleterious germline *BRCA*1and *BRCA*2 mutations will require tumor testing to identify an additional percentage of patients who may benefit from iPARP. Most women with advanced stage epithelial ovarian cancer will have a relapse of their disease and will require additional treatment despite initial therapy. The introduction of poly (ADP-ribose) polymerase inhibitors (PARPi) has resulted in a major change in the approach to epithelial ovarian cancer throughout the treatment life cycle.

Translating recommendations into decisions made in clinical settings involves processes aimed at modifying the behavior of users of consensus recommendations. Health care institutions and patients will follow the recommendations contained therein if they are adequately aware of them and could apply them. In the context of consensus implementation, the following are identified as the main barriers to the application of the recommendations of restrictions on patients' access to health care services, whether due to lack of timely care, delays in authorizations, failure to enroll, economic restrictions or inability to pay, denial of authorizations or refusal to provide services and medicines, lack of knowledge about genetic profiling of patients with epithelial ovarian carcinoma by the first level of care and barriers during the referral and counter-referral process between related specialties.

Interventions aimed at overcoming barriers include distribution of printed and/or digital educational materials;academic training activities with the participation of local opinion leaders;socialization activities with patient participation, dissemination in mass media and written materials in scientific journals and national academic publications and coordination with national health authorities to define actions to implement the consensus recommendations.

Finally, we will seek to define a follow-up and evaluation plan for the process of implementing the recommendations, which will make it possible to evaluate the impact on the outcomes of patients with epithelial ovarian carcinoma in the country by generalizing genetic profiling.

Limitations of this Consensus

The accelerated appearance of new markers of clinical interest in the pathologies treated by this consensus could in the short to medium term modify some of the recommendations and the appearance of new target therapies could change the recommendations in one direction or another. The literature search was limited to PubMed and GIN (Guidelines International Network). The primary evidence on which the CPGs are based was not used, although the CPGs were graded using the AGREE II instrument. Since this is an expert consensus, the risk of subjectivity in the opinions is always implicit.

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Supplentary Appendix

Additional information about this article is available in the Supplementary Appendix.

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