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Review

Prevention, Screening, Treatment and Follow-Up of Gynecological Cancers: State of Art and Future Perspectives

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Abstract

Objective: This study aims to analyze the available data on prevention and early diagnosis in gynecological cancers. **Mechanism**: A comprehensive search was performed in the PubMed (MEDLINE), EMBASE, SCOPUS and Web of Science databases. **Findings in Brief**: To date the prevention programmes of all degrees exist exclusively for cervical cancer. Human Papilloma Virus (HPV) vaccination prevents from infection and development of precancerous lesions and contributes significantly to the deflection of the incidence of cervical cancer. Screening for HPV-related lesions is worldwide performed by cervical smear (Pap-test) and HPV test. Finally, tertiary prevention is aimed at the treatment of previously diagnosticated lesions with the aid of surgery, chemotherapy, radiotherapy and immunotherapy. Unfortunately, to date the prevention programmes of other gynecological tumors have not reached a good performance; indeed, the primum movens that leads to the development of such neoplasms has not been identified yet. Actually, no screening programs for the early diagnosis of endometrial cancer are available, however, it is recommended the adoption of a healthy lifestyle and a balanced diet. Diagnostic biomarkers would be helpful for screening asymptomatic high-risk women, but histopatological examinations remain the gold standard for diagnosis of endometrial cancer. Similarly, there are no screening tests for the diagnosis of ovarian cancer. In recent years many steps forward have been made in this field and new perspectives have been presented, however, additional investigation is needed to optimize the duration and timing of treatment, examine its cost-effectiveness, and identify potential tumor or host biologic factors predictive of the efficacy and adverse events. Finally, there are no primary and secondary prevention for vulvar cancer so patients should be invited to self-examination and pay attention to the presence of symptoms. **Conclusions**: Are the available screening programs for the diagnosis of gynecological carcinomas sufficient? The prevention and the diagnosis of precancerous lesions is the goal to be achieved for all gynecological cancers in order to improve patient outcomes, reduce the costs for managing the disease and prolonged follow up.

Keywords: gynecologic oncology; cancer prevention; gynecological cancers; HPV vaccination; screening programs

1. Introduction

Cancer is still nowadays the second leading cause of death worldwide with about 9.6 million deaths per year [1]. The total and specific incidence for each type of cancer has been growing for several decades [1]. This could be connected to a longer average life expectancy and to an increased exposure to potential risk factors [1]. Recently, 2020 comprehensive global cancer statistics published by the International Agency for Research on Cancer stated that gynecological malignancies accounted for 15.25% out of 8.2 million estimated new cancer cases in women overall [1,2]. Of all these cases, cervical cancer is the 6.5%, endometrial cancer is the 4.5%, ovarian cancer is the 3.4% and vulvar cancer is the 0.85% [2]. Gynecological cancers represent an ongoing source of concern, due to their still too high incidence and cancer-related mortality [3–5]. Specific protocols are applied in order to decrease incidence and development of these cancers. In general, there are three possible steps for managing any kind of cancer, namely primary, secondary, and tertiary prevention. Primary prevention consists in avoiding the disease before it occurs. Lifestyle changes, vaccines and prophylactic treatments are the most explanatory examples of this first step. Secondary prevention consists in detecting and treating the

disease before its open clinical manifestation, in order to improve patients' outcomes. Screening programs fall into this category. The fundamental principle of cancer screening is the detection of the disease at an early curable stage in asymptomatic, apparently healthy population [6]. Finally, tertiary prevention consists in managing active or chronic diseases to prevent complications or irreversible damages [7–14]. Despite the high interest in research, prevention and recent therapeutic innovations introduced in the clinical practice, the prognosis of gynecological cancers remains poor [6–10]. In fact, prevention and early detection of gynecological cancers are not always applicable. In particular, screening tests which are used at present are not very useful in the detection of ovarian cancer and also of endometrial cancer [15]. Another point that must be highlighted concerns the suboptimal adherence to recommended screening programs. Women are not always aware of the importance of prevention [16]. This situation occurs in high-income countries, and it's significantly higher in low-income countries. Consequently, women in low-income countries are disproportionally impacted by cancer's incidence and mortality [17]. The purpose of this study is to analyze the data available in literature on prevention and early diagnosis in gynecological cancers. We sought to provide an update on prevention protocol programs currently available for various gynecological cancers.

2. Materials and Methods

Studies available in the literature on the prevention, screening and treatment of patients with gynecological cancers until February 2023 have been screened. No time limits for research have been selected and all types of articles in the English language have been included. A comprehensive search was performed in the PubMed (MEDLINE), EMBASE, SCOPUS and Web of Science databases. The keywords systematically searched were the following: "vulvar cancer" OR "vulvar tumor" OR "vulvar neoplasm" OR "vulvar malignancy" AND "endometrial cancer" OR "endometrial tumor" OR "endometrial neoplasm" OR "endometrial malignancy" AND "ovarian cancer" OR "ovarian tumor" OR "ovarian neoplasm" OR "ovarian malignancy" AND "cervical cancer" OR "cervical tumor" OR "cervical neoplasm" OR "cervical malignancy" AND "prevention" AND "screening" AND "treatment". Any disagreement between them over the eligibility of particular articles was resolved through discussion with a third (external) collaborator.

3. Results and Discussion

3.1 Cervical Cancer Prevention

Cervical cancer (CC) represents a major health problem due to its still too high incidence, especially in developing countries, where it accounts for the majority of the gynecological cancers and is still the leading cause of cancer deaths among women [18–20]. In developed countries, instead, the diffused use of primary and secondary prevention [10] has enormously decreased the incidence of cervical cancer [21,22]. As for primary prevention, Human Papilloma Virus (HPV) vaccine protects from infection or at least reduces persistence of HPV infection [23]. This vaccine also reduces the development of precancerous lesions and significantly contributes to deflecting the incidence of cervical cancer. HPV vaccine represents the most cost-effective public health measure against cervical cancer. For this reason, it may be considered the key pillar for the prevention of invasive cervical cancer [8]. The most relevant issue concerning this primary prevention protocol is the lack of its general acceptance, despite the efforts made to facilitate and support the diffusion of vaccination. HPV vaccine is currently recommended for routine vaccination in girls and boys at 11 or 12 years of age, even though it could be administered at 9 years [24,25]. Routine prophylactic vaccination should be recommended at 11–12 years of age to ensure its effectiveness before sexual activity [26]. There are currently three types of vaccines available (bivalent, quadrivalent, and nonavalent) which can target at least the two most oncogenic virus genotypes (HPV 16, 18), responsible for over 70% of cervical cancers [26]. As reported by the World Health Organization (WHO) "*One-dose Human Papillomavirus vaccine offers solid protection against cervical cancer*" [27]. However, the number of doses required to make the vaccine effective in terms of protection from HPV infection is objective of study [28,29]. As for secondary prevention, screening is performed through cervical smear (Pap-test) and HPV-DNA test. The main benefit of these screening protocols is a dramatic increase in the diagnosis of cervical dysplasia and consequently its treatment. However, the difference in the availability of such screening between industrialized and developing countries is still crucial. This is shown by the percentages of women undergoing screening, which range from 31% in African countries to 93% in the UK [30,31]. This means that there are large disparities in incidence and mortality resulting from cervical cancer, both regionally and globally [31,32]. Obviously, the stage at diagnosis is also different between industrialized and developing countries, in fact in Western Countries cervical cancer is diagnosed for the major part in the initial stage (International Federation of Gynecology and Obstetrics (FIGO) I–II) mainly thanks to the application of primary and secondary screening programs [30–32]. It's evident that an effort is necessary to try to reduce the prevention gap between these two kinds of countries. It is known that pap-test has not a high grade of sensitivity (about 40%). In order to overtake this gap in sensitivity, HPV-DNA molecular testing was added to Pap-test. This combination reached a sensitivity about 90%. Another important fact is that neither HPV-DNA nor Pap-test can predict patients' risk of progression [32–34]. The use of self-sampling is a valid alternative to

these "conventional" tests and it is already used by some countries to increase cervical cancer screening [35,36]. The self-sampling in pandemic times has also been an important instrument to increase coverage [37,38]. This form of collection is useful in cases where screening is done by molecular tests for HPV detection [39]. Researches in order to fill this gap, individuated new possible strategies as the evaluation of specific cervical cancer biomarkers or the use of automatic visual inspection by artificial intelligence [34,40,41]. It is still important to remember the use of other alternatives for cervical cancer screening based on visual inspection, which is still used in some Countries, albeit with lower accuracy rate [42–45]. Some researches, instead, have focused on protein biomarkers. Those could identify a possible progression from pre-invasive lesions to invasive lesions. In particular, low molecular weight protein bound to cyclin dependent kinase 4 and 6 (p16INK4a) and Marker of Proliferation (Ki-67) seem to detect the uncertain diagnosis of Atypical Squamous cells of Undeterminated Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (L-SIL) [34]. It is also important to mention methylation markers as promising for use in screening stages for cervical cancer after positive screening for high-risk HPV [46–48]. p16INK4a is a tumor-suppressor protein with a role in the regulatory pathway of Cdk-Rb-E2F preventing retinoblastoma protein (pRb) phosphorylation by inactivation of Cyclin-dependent kinases (Cdk)-4/6 [32,34]. p16INK4a immunohistochemical analysis has demonstrated its positivity in almost all cases of high-grade cervical intraepithelial neoplasia instead of its negativity in L-SIL with low-risk human Papilloma Virus (LR-HPV). This differentiation could be useful to distinguish cervical intraepithelial neoplasia positive (CIN+) from L-SIL. Moreover, p16INK4a immunohistochemistry contributes to identify L-SIL lesions associated with high-risk human Papilloma Virus (HR-HPV) types capable of progression [34]. Ki-67 is a nuclear protein associated with proliferation and progression in cells. In fact, it could be considered as a progression/proliferation marker. Immunoistochemical analysis shows high proliferative Ki-67 activity in HR-HPV infection. Instead low proliferative activity is shown in LR-HPV infection [34].

This could be an important difference in order to differenciate high risk of progression of diseases instead of low risk.

Because of this data collected in literature, p16INK4a and Ki-67 immunoistochemistry have been proposed as biomarkers which could evaluate progressive cervical lesions from cervical dysplasia and detect high-risk precursor [34]. Further studies will be needed in order to confirm the role of the above-mentioned biomarkers, and to make screening more reliable. Finally, tertiary prevention aims at the treatment of previously diagnosticated lesions with the aid of surgery [49–52], chemotherapy, radiotherapy and immunotherapy [53]. The treatment of this type of neoplasm differs according to the stage at which the disease is diagnosed, in fact for very early stages (according to the International Federation of Gynecology and Obstetrics classification, FIGO IA1) conservative treatment can be proposed young patients and desirous of offspring; in patients with FIGO stage IA2, IB and IIA the mainstay treatment is radical hysterectomy with bilateral salpingo-oophorectomy (BSO) and lymph node assessment performed with open laparotomy plus adjuvant radiotherapy (RT) with or without chemotherapy (cisplatin–5-fluorouracil) for four courses [52,54–57]; instead a combined chemo-radiotherapy approach is indicated for the treatment of cervical tumors in advanced stages [54]. Although researchers have made so many steps forward, additional therapies for women with node-positive locally advanced and metastatic cervical cancer are still necessary. A novel strategy capable of improving outcomes in patients with cervical cancer could be immunotherapy, particularly immune checkpoint blockade. Adoptive T-cell therapy and immune checkpoint inhibition have exhibited encouraging rates of response and durable survival for women who have failed standard therapies. Since immunotherapy could be combined with chemoradiation, evidence shows that there is a chance to improve local control as well as to enhance systemic response. There are several ongoing prospective trials which are currently aiming to expand existing knowledge of the immune system and its role in combating malignancy, through the investigation of the optimal timing and dosing of immunotherapy [58]. Another point to underline is that the risk of recurrence/persistence of cervical pre-cancerous lesions is increased in patients with previous cervical intraepithelial neoplasia (CIN). Several studies suggested post-surgical recurrent disease both in women and men exposed to previous HPV infection can be dramatically reduced by HPV vaccination [26,59–61]. In this sense, it is possible to state that HPV vaccination is protective even for CIN recurrence/persistence, so patients after primary treatment deserve an accurate follow-up and information on the benefits of adjuvant vaccination [59]. Further large-scale randomized controlled studies are required to confirm these findings and drive adjuvant HPV vaccine into routine clinical practice.

3.2 Endometrial Cancer Prevention

Differently from Cervical Cancer, there is no screening for early diagnosis of endometrial cancer (EC); this is due to the fact that, at the moment, clinical practice guidelines do not recommend screening for endometrial cancer in the general population [62]. In general, since risk factors for the development of EC are well known (i.e., metabolic syndrome, obesity, diabetes, arterial hypertension), it is recommended the adoption of a healthy lifestyle and a balanced diet. Although the absence of a specific prevention program, EC is diagnosed for more than 90% of cases at an early stage [62,63]. This happens thanks to an early

clinical manifestation of worrying symptoms, like abnormal uterine bleeding in postmenopausal age [62,64]. As a matter of fact, abnormal vaginal bleeding is the most common symptom referred by up to 90% of women with EC. In any case, abnormal vaginal bleeding not necessarily is associated with EC, since blood loss could be due to various benign pathologies. A detailed patient history generally helps in understanding a patient's cancer risk and the need to proceed in further investigation and care, like transvaginal ultrasound, with measurement of the endometrial thickness and/or endometrial sampling through hysteroscopy or biopsy [64–66]. Diagnostic biomarkers would be helpful for screening asymptomatic high-risk women, since histopathological examinations remain the gold standard for diagnosis of endometrial cancer as there are still no valid non-invasive bio-markers or any panel of biomarkers that might accurately predict the presence and extent of endometrial cancer [67–69]. For this reason, researchers have examined cancer antigen 125 (CA 125) and Human Epididymis Protein 4 (HE4), and body mass index (BMI) in an associated model, to identify subjects affected by EC with good accuracy [70,71]. However, this is not enough, because single or paired tumor markers still do not have enough sensitivity and specificity to diagnose this tumor, so they are commonly used only as markers of recurrence during the follow-up [72]. This means that further investigation is needed, in order to improve EC prevention protocol.

3.3 Ovarian Cancer Prevention

Screening tests for the diagnosis of ovarian cancer (OC) represent a real challenge at the moment. Even for OC there are no well-structured prevention programs but, unlike the tumors already discussed, this cancer is often asymptomatic until an advanced stage, so very frequently the diagnosis is delayed and the prognosis is poor. The high mortality rate of this cancer is also influenced by its high recurrence rate and by surveillance and prophylactic treatment programs only for high-risk women, with genetic mutations and family syndromes associated with high incidence of OC (breast cancer gene (BRCA) mutations and Homologous Recombination Deficiency (HRD)) [73–76]. Although tumor markers historically only played a role in the follow up of OC, a recent review highlighted the superiority of HE4 and CA 125 tumor markers in the timely diagnosis of this neoplasm compared to the use of nuclear magnetic resonance (NMR) and of Risk of Ovarian Malignancy Algorithm (ROMA) algorithm [73]. In fact, literature currently reports that one of the best biological diagnostic tools to predict the risk of ovarian cancer in patients with suspected benign ovarian tumors, seems to be a combination of CA 125 and HE4 levels. If the levels of CA 125 and of HE4 increase, it is very likely that we are in the presence of a malignant lesion [73]. This would lead to consider the need of a surgical treatment for an anatomopathological examination. Differently, a simple ultrasound or biological monitoring may be considered, if one of the markers was above the cut-off as long as the other was below the cut-off specified. It is also necessary to take into consideration that HE4 levels increase with advancing age, so it might be important to evaluate algorithms which consider the patients' age and not her menopausal status. Another important information to be considered and recorded in the patient's clinical history, is that serum HE4 levels vary in smokers and in hormonal contraceptive users [77,78]. In recent years many steps forward have been made in this field and new perspectives have been presented as the use of circulating tumor DNA and circulating microRNA profiling [77,78]. Circulating tumor DNA (ctDNA) is found in primary tumors or metastatic lesions. ctDNA could be extracted by patient's plasma or serum. It can be used as for detecting an early diagnosis and for monitoring the treatment response [77,78]. It has been reported that if ctDNA persists in treated ovarian cancer survivors it suggests a poor clinical prognosis. Also is seen that it has a higher sensitivity than CA 125 [77]. ctDNA's genetic mutations are the same DNA defects of the primary tumor. Thus, the ctDNA detection could be used for early diagnosis and staging of cancer, tumor efficacy evaluation, tumor recurrence monitoring, and prognosis evaluation [77]. Anyhow, more studies are needed in order to confirm the role of this possible new weapon in screening.

The gold standard of treatment for OC is cytoreductive surgery plus platinum-based chemotherapy. Anyway, 80% of patients with advanced disease will experience recurrence in 5 years from the diagnosis [79,80]. In order to face this difficulty researchers analized new strategies of treatment. As reported in literature, angiogenesis inhibitors could represent a valuable option of treatment. Bevacizumab, is a humanized monoclonal immunoglobulin G (IgG) antibody that targets vascular endothelial growth factor A (VEGF-A). This drug blocks the binding to VEGF-1 and VEGF-2 receptors. As a consequence, bevacizumab could inhibit tumor growth [78]. Bevacizumab is approved as first- and second-line treatment for advanced epithelial ovarian. Despite its use with favorable results, there still exists disagreement on its employment [81]. Bevacizumab usage after platinum/taxel related chemotherapy showed an increase of Progression Free Survival (PFS) in patients with advanced OC. However, additional studies are needed in order to standardize the duration and the strategic timing of treatment [78].

3.4 Vulvar Cancer Prevention

Finally, vulvar carcinoma is a rare tumor, usually with asymptomatic or nonspecific presentation, which frequently occurs on benign/inflammatory lesions and whose management is mainly surgical both in advanced and early stages [82–85]. Two premalignant types of precancerous vulvar lesions have been identified: vulvar intraepithelial

neoplasia (VIN) related to HPV and VIN associated with vulvar dermatosis, such as lichen sclerosus [86,87]. The treatment of vulvar cancer principally involves a surgical approach; this can be used alone for early-stage tumors or combined with neoadjuvant therapy for advanced or larger tumors [83,88]. It is also necessary to assess the status of lymph nodes with sentinel node biopsy or with lymphadenectomy (both mono or bilateral) based on the suspicion of positive lymph nodes [89,90]. Chemotherapy and radiotherapy are more often used as adjuvant treatment of vulvar cancer, principally for the prevention of local and loco-regional recurrence [91]. Primary prevention by HPV vaccination is possible for this tumor, but only lesions associated with virus infection are prevented. There is no secondary prevention, in fact more than 30% of these tumors are dignosticated in advanced stage, so patients should be invited to self-examination and to pay attention to the presence of itching, burning, change of pigmentation or the development of ulcers at the vulvar area [92–94].

4. Conclusions

Can we say that available screening programs for the diagnosis of gynecological carcinomas are sufficient? Unfortunately, the answer to this question cannot but be negative. Consolidating existing programs and trying to develop new ones as quick as possible is essential. New perspectives in screening are the best strategy we can count on, if we consider the aim of reducing incidence and mortality. The prevention and the diagnosis of precancerous lesions is the goal to be achieved for all gynecological cancers in order to improve patient outcomes, reduce the costs for managing the disease and prolonged follow up. Further strong economic commitments are necessary for screening programs to be accessible to all women and to be properly and systematically applied in all countries.

Author Contributions

TGD, OD and AG designed the research study. GB and CDD performed the research. ASL, VC and EV analyzed the data. VDD, MGS and DC wrote the manuscript and contributed to interpretation of data for the work. LM and VDD supervisioned and contributed to data acquisition and analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest. Andrea Giannini, Antonio Simone Laganà, Violante Di Donato and Ottavia D'Oria are serving as one of the Guest editors of this journal; Andrea Giannini, Antonio Simone Laganà, Donatella Caserta and Ludovico Muzii are serving as one of the Editorial Board members of this journal. We declare that Andrea Giannini, Antonio Simone Laganà, Violante Di Donato, Donatella Caserta, Ludovico Muzii and Ottavia D'Oria had no involvement in the peer review of this article and have no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Michael H. Dahan.

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