

Cervical cancer: a systematic review

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RESUM

El càncer és un terme designat a un ampli ventall de malalties que presenten una característica en comú: la multiplicació ràpida i descontrolada de cèl·lules anormals. El càncer ginecològic es localitza en els òrgans del sistema reproductor femení, tals com els ovaris, l'úter, el cèrvix, la vagina i la vulva. Segons el Global Cancer Observatory (GCO), el càncer és la segona causa de mortalitat mundial, atès que causa 1/6 defuncions; majoritàriament, la displàsia cervical es dona en dones d'entre 20 i 30 anys, encara que les defuncions en pacients menors de 30 anys són casos aïllats (The National Cancer Institute [NCI], 2021). A escala mundial, de les cinc possibles regions on es pot originar un càncer ginecològic, la cervical, és el que major incidència presenta, seguit de l'úter i l'ovari; concretament l'any 2020 es van registrar un total de 3,1% de nous casos de càncer cervical (The Global Cancer Observatory [GLOBOCAN], 2020). L'aparició de tumors ginecològics pot estar relacionada amb alguns factors de risc, com l'estil de vida o les infeccions externes (p.ex., la produïda pel virus del papil·loma humà (HPV) (GLOBOCAN, 2022); també poden ser conseqüència de factors genètics, tals com els polimorfismes de nucleòtids simples (SNPs). L'objectiu d'aquest TFG és dur a terme una revisió sistemàtica dels factors que poden originar el càncer cervical, ja siguin genètics o externs. També s'han abordat les principals característiques del desenvolupament d'aquest càncer ginecològic, i es descriuen els principals mètodes de diagnòstic i tractament. Amb aquesta finalitat, es van definir els criteris d'inclusió i exclusió en una taula de PICOS (Population, Intervention, Comparator, Outcome, Study) i es va realitzar una recerca bibliogràfica a través de MEDLINE-PubMed fins al gener del 2022; a partir d'aquesta selecció, es van incloure un total de 68 articles. Els resultats van indicar que, majoritàriament, el desencadenant causant d'aquesta malaltia és la variació genètica juntament amb factors externs. A més, es va confirmar el paper tant rellevant que desenvolupa el component genètic dels individus pel diagnòstic, tractament i control del càncer de cèrvix. Malgrat tot, cal més investigació, així com una actualització de les tècniques de tractament i diagnòstic, per tal de reduir la incidència i la mortalitat d'aquesta malaltia.

Paraules clau: càncer cervical, biomarcadors, diagnòstic, tractament, factors de risc, virus del papil·loma humà.

RESUMEN

El cáncer está asociado a una amplia variedad de enfermedades que presentan la misma característica: la multiplicación rápida y descontrolada de células anormales. El cáncer ginecológico se localiza en los órganos del sistema reproductor femenino, tales como los ovarios, el útero, el cérvix, la vagina y la vulva. Según el Global Cancer Observatory (GCO), el cáncer es la segunda causa de mortalidad mundial, y causa aproximadamente 1/6 defunciones; mayoritariamente, la displasia cervical se da en mujeres entre los 20 y 30 años, aunque las defunciones en pacientes menores a 30 se consideran casos aislados (The National Cancer Institute [NCI], 2021). A nivel mundial, de las cinco posibles regiones donde se puede originar, el cérvix es la que presenta una mayor incidencia, seguida del útero y el ovario; concretamente en el año 2020 se registraron un total de 3,1% de nuevos casos de cáncer cervical (The Global Cancer Observatory [GLOBOCAN], 2020). La aparición de tumores ginecológicos puede deberse a distintos factores de riesgo, tales como el estilo de vida o las infecciones externas (p.ej. la producida por el virus del papiloma humano, VPH) (GLOBOCAN, 2022); también pueden ser consecuencia de factores genéticos, tales como los polimorfismos de nucleótidos simples (SNPs). El objetivo de este TFG es la revisión sistemática de los factores causantes del cáncer cervical, ya sean genéticos o externos. También se aborda el desarrollo de este cáncer ginecológico, y se describen los métodos de diagnóstico y tratamiento. Por este motivo, se definieron los criterios de inclusión y exclusión en una tabla de PICOS (Population, Intervention, Comparator, Outcome, Study) y se realizó la búsqueda bibliográfica mediante MEDLINE-PubMed hasta enero del 2022; a partir de esta selección, se incluyeron un total de 68 artículos. Los resultados indicaron que, habitualmente, el causante de esta enfermedad es la variación genética junto con factores externos. Asimismo, se confirmó el papel relevante del componente genético de los individuos para el diagnóstico, tratamiento y control del cáncer de cérvix. Con todo, es necesario que, para reducir la incidencia y la mortalidad de esta enfermedad, se lleven a cabo más estudios así como una actualización de las técnicas de tratamiento y diagnóstico.

Palabras clave: cáncer cervical, biomarcadores, diagnóstico, tratamiento, factores de riesgo, virus de papiloma humano.

ABSTRACT

Cancer is a concept that describes a wide number of diseases which present the same trait: a fast, uncontrolled proliferation of abnormal cells. The gynaecological cancer is localised in the organs of the female reproductive system, such as the ovary, the uterus, the cervix, the vagina, and the vulva. According to the Global Cancer Observatory (GCO), cancer is the second cause of mortality in the World, as approximately 1 out of 6 deceases is caused by this disease; cervical dysplasia is mostly detected in women between 20 and 30 years old, although deceases of youngers than 30 are considered isolated cases (The National Cancer Institute [NCI], 2021). On global scale, out of the fives possible regions where gynaecological cancer can appear, the cervix is the one having the most incidence, followed by the uterus and the ovary; in particular, in 2020, 3.1% new cases of cervical cancer were registered (The Global Cancer Observatory [GLOBOCAN], 2020). Diverse risk factors, such as lifestyle and external infections - like the one produced by the Human Papilloma virus (HPV) (GLOBOCAN, 2022) -, may produce gynaecological tumours; this disease could also be a consequence of genetic factors, such as single nucleotide polymorphisms (SNPs). The aim of this Dissertation is to review systematically the factors that may underlie cervical cancer, either these are genetic or external factors. In addition, how this cancer develops is approached together with the methods of diagnosis and treatment. For this purpose, the inclusion and exclusion criteria were defined in a PICOS (Population, Intervention, Comparator, Outcome, Study) table and a literature search was conducted through MEDLINE-PubMed until January 2022; based on this selection, a total of 68 articles was included. Results indicated that the source that originates cervical cancer is mostly the genetic variation along with environmental factors. In conclusion, the genetic component in individuals was found to be relevant for the diagnosis, treatment and monitoring of cervical cancer. In spite of all the aforementioned, further research and an update on treatment and diagnosis are needed to reduce the occurrence and mortality of this disease.

Keywords: cervical cancer, biomarkers, diagnosis treatment, risk factors, human papilloma virus.

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1. INTRODUCTION

1.1 Cervix and cervical cancer

According to the National Cancer Institute (NCI), in the anatomy of the female reproductive system, the cervix is “the lower, narrow end of the uterus that forms a canal between the uterus and vagina” (Fig. 1) (NCI, 2022).

Cervical cancer usually develops slowly over time; before cancer appears in the cervix, dysplasia, which consists of the appearance of abnormal cells in the cervical tissue, occurs. Thereafter, these abnormal cells may become cancer cells and start to grow and spread more deeply into the cervix and surrounding areas (NCI, April 2022).

Tumours can be classified based on their origin, they could begin in squamous cell (squamous cell carcinoma), which is found in the tissue that lines the cervix (Fig. 2) or in glandular tissue (adenocarcinoma), which lines certain internal organs and makes and releases substances (Fig. 3), or it could even be an adenosarcoma, which is a mixture of an adenoma and a sarcoma; the sarcoma begins in bone or in the soft tissues of the body (NCI, June 2022). Remarkably, the type of tumour conditions the treatment, which can be personalized to the patient. It is worth mentioning that main institutions and organizations, such as FIGO (The International Federation of Gynecology and Obstetrics), IECC (International Endocervical Adenocarcinoma Criteria and Classification), WHO (World Health Organization) and GCO, agreed on the same classification regarding whether a given tumour must be considered a squamous cell carcinoma or a cervical adenocarcinoma.

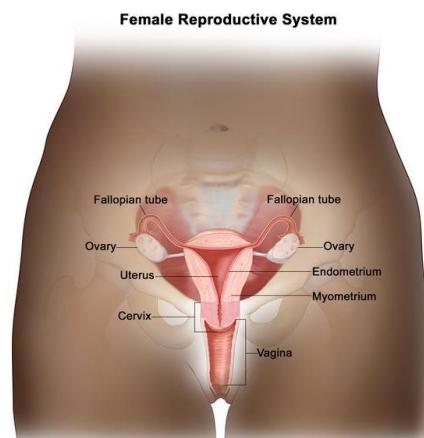


Fig. 1. *Female Reproductive System*, Terese Winslow LLC, 2021. Terese Winslow LLC, Medical And Scientific Illustration. Available at: <https://www.teresewinslow.com/urogenital-reproductive>

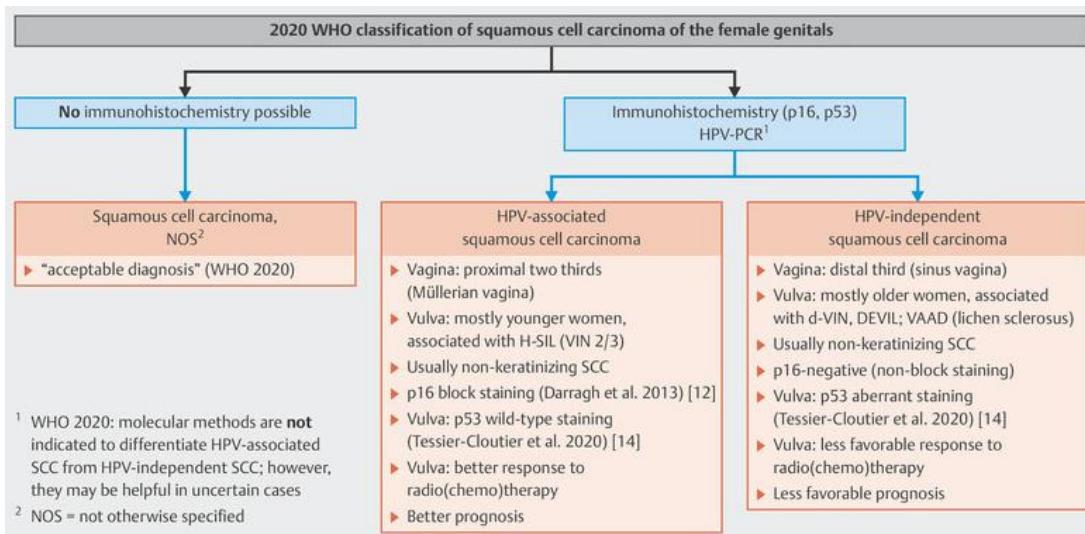


Fig. 2. 2020 WHO classification of squamous cell carcinoma in the female genitals. From: Höhn et al., 2021.

Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8494521/>

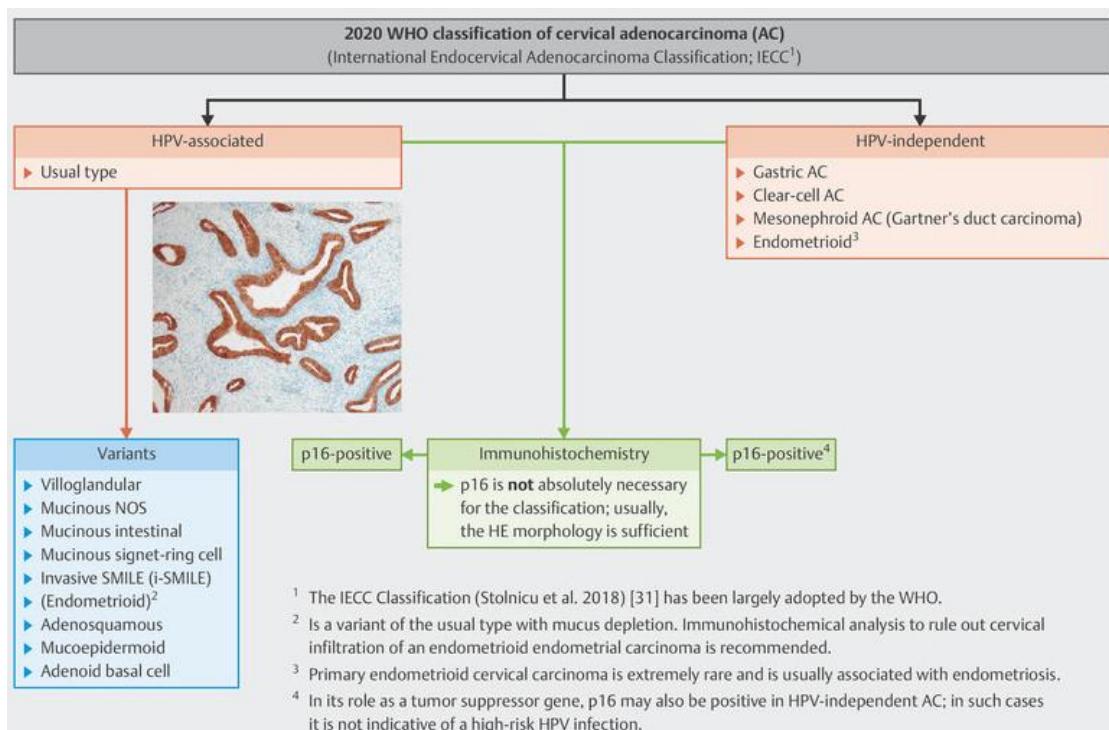


Fig. 3. 2020 WHO classification of cervical adenocarcinoma (IECC). From: Höhn et al., 2021. Available:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8494521/>

1.2 Staging system

After a cervical cancer is diagnosed, tests are done to find out if cancer cells have spread within the cervix or other parts of the body; the process used to determine if cancer has spread is called staging (NCI, April 2022). The cervix was the first organ to be assigned a clinical staging system for cancer by FIGO in 1958 (Bhatla et al., 2021); the staging of the cancer of

cervix uteri is as important as its classification, because according to these factors, treatment and prognosis can be tailored specifically to each individual case.

1.3 Cervical cancer factors

The underlying causes for cervical cancer could be divided into a) genetic factors, such as certain alleles (Hu et al., 2018), single nucleotide polymorphisms (SNP) in determined genes (Charles et al., 2020; Thakur et al., 2019; Pandey et al., 2019; Phuthong et al., 2020; Wu et al., 2017; Wongpratape et al., 2020; Ainiwaer et al., 2020; Łażniak et al., 2017; Haque et al., 2020; Pereira et al., 2020; Niu et al., 2017; Gao et al., 2020; Wang et al., 2020; Lutkowska et al., 2017; Huang et al., 2020), the family history of cervical cancer (Pereira et al., 2020) and the immune system state (Phuthong et al., 2020); and b) external factors. Regarding the latter, the human papilloma virus (HPV) (Tan et al., 2018; Dong et al., 2019) is an infectious agent that causes most of the cancer cases in women, as indicated by GCO; in 2018, an estimated 56.1% of cancer cases in females were caused by the infection of this virus, followed by *Helicobacter pylori* (de Martel et al., 2020).

In spite of this, the virus alone is not sufficient to promote carcinogenesis; in effect, environmental factors, such as diet habits (overweight), smoking, hormonal oral contraceptives, and parturition, and social factors, like low income and limited access to health care, also play a crucial role in cervical cancer development (Pereira et al., 2020). It is becoming apparent that the interplay between the intrinsic factors of CC (Cervical Cancer) development and environmental factors also influences disease manifestation and its clinical course (Zidi et al., 2020).

1.4 Diagnosis and treatment

Cervical cancer is largely preventable with appropriate screening and follow-up, as precancerous lesions can be found prior to invasion, yet women continue to develop this disease (Benard et al., 2021).

Even so, availability of an accurate and predictable early screening of cervical cancer is urgent, as the prognosis of early cervical cancer is better for the survival rate and the recurrence rate after radical operation. At present, the poor prognosis of CC is mainly due to late FIGO staging, large tumour volume, deep interstitial infiltration, vascular tumour thrombus, and lymph node metastasis (Chen et al., 2019). That is the reason why the use of existing or the development of new tailored interventions in unscreened women could increase the number of

diagnosed cases, thus having a great potential in decreasing the burden of this disease (Benard et al., 2021).

The detection of useful biomarkers that may assist in disease management is one of the main fields to research; for instance, tumour biomarkers in serum are of great significance in the treatment of CC patients (Chen et al., 2019). Important, discovered local tumour prognosticators are the pattern of HPV type, the infection condition, and the presence of lymphovascular invasions (Stolnicu et al., 2021; Tan et al., 2018). Additionally, certain biomarkers are decisive for the prognosis of CC patients; the identified ones on the included articles are specific circular RNAs (He et al., 2020) and microRNA (Thakur et al., 2019; Du et al., 2020; Ma et al., 2019), the identity of histone modifications (Beyer et al., 2017), certain SNPs that affects specific genes and the sequences of particular cytokines and the receptors.

Besides the aforementioned biomarkers, cancer screening programs, the health care system, and education strategies and communication interventions require to be continuously innovated among developing countries primarily. These are the primary health care strategies that could motivate women to overcome psychological and health care barriers and improve cervical cancer knowledge and screening, which are the principal factors that explain the high rate of cervical cancer in many countries. In addition, this knowledge about cervical cancer could also encourage vaccination programs to prevent HPV infection (Dong et al., 2019; Lamb et al., 2018; Getahun et al., 2019; Murewanhema, 2021).

The workable treatments that are currently applied are chemoradiotherapy (CRT) (Kushwah et al., 2020); radiotherapy (RT); treatments based on the administration of drugs or targeted therapy, for instance lapatinib (Burk et al., 2017), cetuximab, paclitaxel, (Pignata et al., 2019) or balstilimab (O'Malley et al., 2021); immunotherapy; surgery, which can consist of hysterectomy, trachelectomy, lymphadenectomy (Alifu et al., 2018), laparoscopic surgery (Wei et al., 2018; Xu et al., 2020); and brachytherapy. Furthermore, treatment could also combine more than one surgical method and another of the aforementioned treatments, including drugs, CRT or RT (Purohit et al., 2020; Sert et al., 2021; Lan et al., 2017; Qian et al., 2017; Shrivastava et al., 2018; Novackova et al., 2020; Nie et al., 2017; Joseph et al., 2020). When cases are diagnosed in late stages, patients are only suitable for palliative care (Tapera et al., 2019).

The choice of these treatment modalities depends on the age of the patient, their desire to have children, and the type and stage of cervical cancer (NCI, April 2022). Regardless of the aforementioned factors, patients are encouraged to have surgery instead of RT, because this

treatment leads to a greater survival rate. In addition, an important indicator for the evaluation of the effects of different treatment modalities on women with gynaecological cancer is the quality of life (QoL) after cancer treatment (Li et al., 2017), as treatments may unfortunately have side effects or long-term sequela.

1.5 Morbidity and mortality rates

According to the GCO and WHO, in 2020, a global incidence of 6.5% cervical-uterine cancer cases was registered; as depicted in Fig. 4, cervical cancer is one of the five cancers that have more incidence in women. Moreover, in the same period of time, approximately 7.7% deaths on account of cervical cancer were estimated in the entire population.

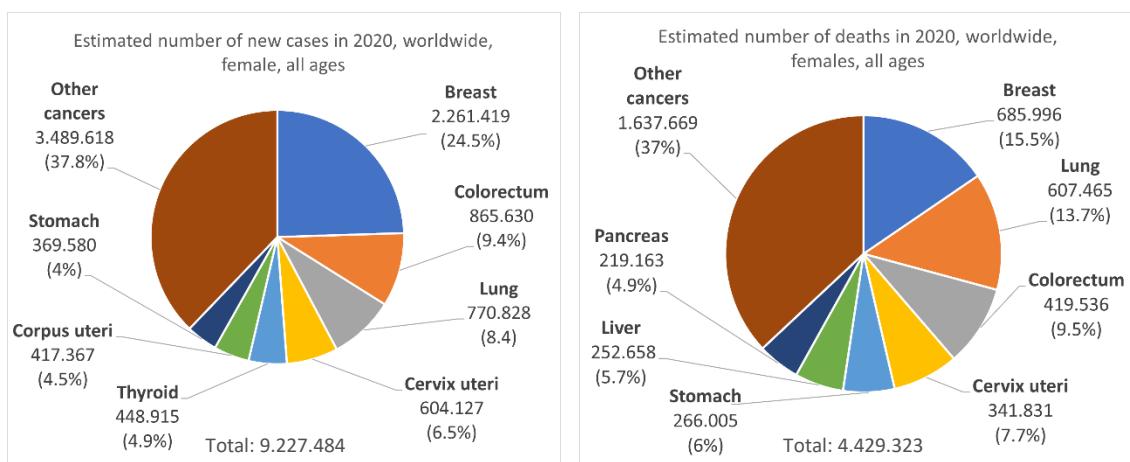


Fig. 4. Estimated number of new cases (left) and deaths (right) of all cancer types in females in 2020. Modified from GLOBOCAN, by International Agency for Research on Cancer 2020. (<https://gco.iarc.fr/>)

The majority of cancer morbidity and mortality occurs in low- and middle-income countries (LMICs), which account for 56% of new cancer cases, 62% of cancer deaths, and 69% of cancer-caused disability adjusted to life years (Global Burden of Disease Cancer Collaboration et al., 2017). The gap in morbidity and mortality between LMICs and high-income countries (HICs) is largely derived from the limited availability of screening and prevention programs (Park et al., 2018).

In LMICs, primary prevention through vaccination and secondary prevention via screening are important public health interventions to reduce the cervical cancer burden. The failure to access preventive services presents the greatest risk factor for the development of invasive cancer (Kuguyó et al., 2017). The challenges of late-stage presentation and limited resources, which prevent more patients from receiving CRT, are the most critical barriers to better patient outcomes (Park et al., 2018).

Additionally, it has been reported that the COVID-19 pandemic has had an adverse impact, especially in these disadvantaged countries; due to the movement restrictions imposed by lockdowns coupled with poor roads and networks, the utilisation of services of health services has been reduced (Tapera et al., 2019). These issues have an implication on the treatment and prevention of CC; a health sector that was reported as fragile at the beginning of the pandemic may emerge weaker and fail to cope with increased disease burden (United Nations Zimbabwe, 2020).

2. AIMS

While most of the opinions and guidelines described above were published more than 5 years ago, new data have become available in scientific database from then on. Hence, the objective of the present study was to systematically review the main findings from the available literature about cervical cancer and to provide an updated, comprehensive assessment of this pathology.

Based on a critical review of the available literature, the specific aims were:

- To identify the genetic and external factors that could originate cervical cancer.
- To set an updated classification and staging of cervical cancer.
- To describe the methods of diagnosis and treatment for cervical cancer patients.
- To collect and summarize the current evidence about biomarkers that could have influence over the development and probability of suffering from a cervical cancer.

3. METHODS

3.1 Data sources and search strategy

The present systematic review was performed by using the MEDLINE-Pubmed (<https://pubmed.ncbi.nlm.nih.gov/>) database, including studies published until 18 January 2022. Fact sheets from the Global Cancer Observatory (GCO) (<https://gco.iarc.fr/>), the most recent FIGO (International Federation of Gynecology and Obstetrics) Cancer Report, published in 2021, and The National Cancer Institute website (<https://www.cancer.gov/>) were also looked up.

In order to define inclusion and exclusion criteria, a PICOS (Population, Intervention, Comparator, Outcome, Study) table was designed prior to the search (Table 1). The search strategy used different key words related to cervical cancer origin, classification, biomarkers, detection, development, and treatment.

Table 1. PICOS design structure, including the inclusion and exclusion criteria and the keywords were used for the definition of the search strategy and the eligibility of the study.

PARAMETER	INCLUSION	EXCLUSION	KEYWORDS
Population	- Human females with cervical cancer.	- Studies in other species	<i>Homo sapiens</i> , human, females
Intervention	- Studying factors that increase the probability to develop cervical cancer (externals and genetics). - Studying how the cervical cancer could develop. - Methods and techniques to diagnose and treat the different types of cervical cancer. - The progress of cervical cancer during the COVID-19 pandemic.	- Studies that evaluate other gynaecological cancers - Studies performed with cell lines.	Cervical cancer, cervical cancer biomarkers, hormonal factors cervical cancer, virus cervical cancer, HPV cervical cancer
Comparison	- Females with cervical cancer (cases) versus healthy females (control). - Different treatments for the same stage of cervical cancer.	- Studies that do not evaluate cervical cancer - Studies with low sample size ($n < 100$) - Studies with high sample size ($n > 1000$)	
Outcomes	- Biomarkers, genetic and external factors associated to cervical cancer. - Stages of cervical cancer. - Treatment for cervical cancer. - How COVID-19 has impacted on cervical cancer care.		Cervical cancer origin, cervical cancer development, external factors cervical cancer, genetic cervical cancer, cervical cancer diagnosis, cervical cancer treatment
Study design	- Classical Articles - Clinical studies - Observational studies - Cross-sectional studies	- Review - Letters - Meta-analyses - Systematic reviews - Commentaries - Case reports	Classical/conventional articles, Clinical Studies, Observational studies, Cross-sectional studies, English abstract, Studies published on the last 5 years, English

3.2 Study eligibility

Eligibility of the different studies for inclusion in the systematic review was determined on the basis of the criteria defined in the PICOS design (Table 1). Articles meeting the following criteria were included: i) studies evaluating the external and genetic-induced factors of cervical cancer, ii) studies performed in humans, iii) studies evaluating the cervical cancer diagnostic, iv) studies analysing cervical cancer biomarkers, and v) comparisons performed between treatments.

Studies evaluating other gynaecological cancers or other types of cancers, and those performed with cell lines were excluded from this Dissertation. Review, letters, meta-analyses, systematic reviews, commentaries, and case reports were considered non-eligible for inclusion.

3.3 Study selection procedure

Study selection for the systematic review was performed in different stages, as depicted in the flowchart shown in Fig. 3. First of all, articles from MEDLINE-PubMed were collected in a Microsoft Excel which included publication date, authors, title, article type, DOI, abstract and publishing journal. The restrictions applied on the search in the PubMed toolkit were i) articles written in English and ii) studies published on the last five years. Studies that were duplicated or not accessible were removed.

As an additional restriction, studies with a sample size of less than 100 members or more than 1,000 members were excluded; the size range was determined according to the sample size chosen on most of the included articles. Afterwards, a selection and classification of articles that were not relevant was done by using the following stages: i) screen by the title, ii) screen by the abstract, iii) studies excluded based on the full text as it was not relevant or not followed the eligibility criteria, and iv) articles included in the systematic review.

Finally, for citations, the tool Mendeley was used to organise the references of research studies, utilizing the correct APA (American Psychological Association) citation format, and fulfilling the copyright statements referring the authors.

3.4 Data extraction for systematic review

After obtaining the final list of included articles, a careful read of each manuscript was conducted to extract the aim of the study, summary of the results and main conclusions, and to classify studies according to their findings regarding the factors that could originate cervical

cancer, the presence or absence of biomarkers related with CC, the classification and development of cervical cancer, and diagnostic methods, or treatment for the cervical cancer.

3.5 Ethical and sustainability criteria

Ethical and sustainability criteria applicable to this systematic review were always taken into consideration. On the one hand, concerning the ethical criteria, all studies were checked for women to have signed the informed consent form for the extraction of the samples, and all the protocols were under the guidelines of the World Medical Association's Code of Ethics for Human Experiments (Declaration of Helsinki).

On the other hand, in terms of sustainability, only computer resources were used; printing papers was avoided. Finally, as this Dissertation was based on a systematic review, it did not require the student to enter the laboratory; neither biological or chemical materials were manipulated, nor was laboratory equipment needed.

4. RESULTS

4.1 Identification and selection of articles

Fig. 5 shows how articles were identified and selected. After an initial search, 4,700 records were identified from the MEDLINE-PubMed database. After a first filter, two duplicated articles were removed, eight were not available and 621 were excluded because of the article type. This resulted in 4,069 articles, which were screened taking into account the title and abstract, leading to the exclusion of 1,404 records, as not meeting the scope of this study or presenting outcomes not relevant to the systematic review. Out of 2,665 articles assessed for eligibility, 2,597 were excluded based on the full text, i) 850 included other types of cancer ii) 920 were conducted in animal models or used cell lines, iii) 768 used *in vitro*, *in vivo* or *in silico* techniques, iv) 59 did not adhere to the population size.

These exclusion steps led to the inclusion of 68 articles, which were declared eligible as they met all the previously defined criteria. After this step, the included records were assorted depending on the subject approached by researchers (origin, classification, biomarkers, development, or treatment of CC).

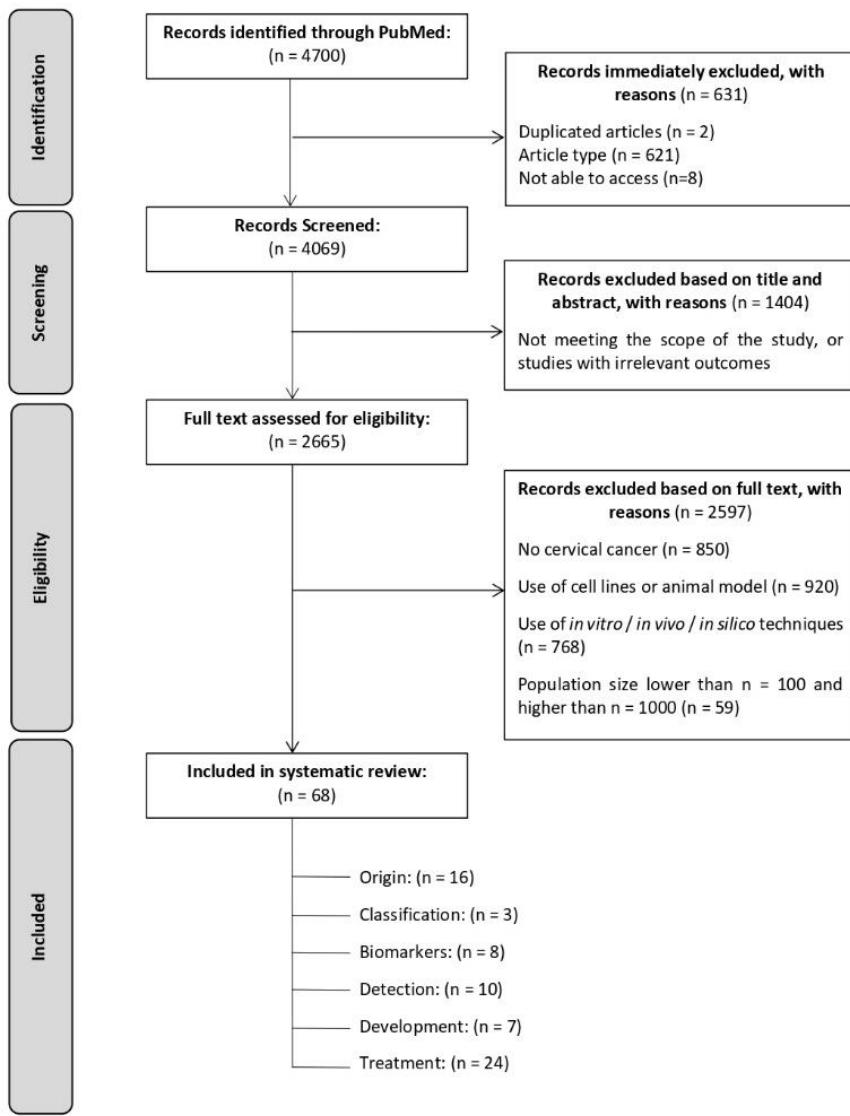


Fig. 5. Flowchart of the literature search and the selection process.

5. DISCUSSION

To the best of the author's knowledge, this is the first systematic review that provides updated information regarding the identification of the cervical cancer associated biomarkers and other factors that could originate this disease. In addition, the assessment of the treatment and the methods of diagnosis were reviewed and, in all cases, the literature search aimed at providing an up-to-date perspective of cervical cancer.

5.1 Factors that could originate cervical cancer

Factors that could cause cervical cancer are divided into external or environmental, and genetic or hereditary. Environmental factors along with altered genetic makeup, are related to disease progression (Gupta et al., 2016)

The persistent infection with high-risk human papillomavirus (hr-HPV) is the leading cause of cervical cancer (Beilner et al., 2021); it is believed to be a major factor in the development of more than 90% of cervical tumours (CT). The mechanism of HPV consists of the infection of the cervical epithelium, thus increasing the risk of premalignant lesions that then progress to a cervical cancer (Zur, 1996). More than 200 types of HPV have been identified to date; while these HPV types can be categorized into either cutaneous or mucosotropic type, only the latter is relevant for the development of cervical carcinoma (de Villiers et al., 2004; Bernard et al., 2010). The majority of women infected with HPV, however, do not develop cervical cancer; this indicates that the infection is not sufficient to induce tumorigenesis (Gimenes et al., 2014).

External factors of CC include smoking habits, pollutants, multiparity, oral contraceptive use, menopausal status, immunodeficiency, immunosuppression, early sexual intercourse, multiple sexual partners, menstrual hygiene, family history, stress-related disorders, and woman age at the time of her first full-term pregnancy (Kushwah et al., 2020; Luhn et al., 2013; Almonte et al., 2008). In fact, the additive effect of smoking habits has been reported, as carcinogenic components of tobacco can be found in the cervical mucus of CC patients (Zidi et al., 2020). Moreover, having multiple sexual partners and the use of hormonal contraceptives should be regarded as risk co-factors for severe cervical dysplasia; therefore, clinicians should be encouraged to recommend patients to avoid the exposition to such factors in order to prevent the CC installation or/and aggravation (Pereira et al., 2020).

It is worth mentioning that during the search of information, most of the originating factors of CC were found to be genetic components; these biomarkers could predict high or low predisposition to develop cervical cancer, help to detect early-stages of the disease, therefore preventing advanced CC stages, and monitor the treatment response.

5.2 Classification and staging

A study by Burk et al. (2017) identified novel genomic and proteomic characteristics that allowed subclassifying cervical cancers; integrated clustering identified keratin-low squamous, keratin-high squamous, and adenocarcinoma-rich clusters defined by different HPV and molecular features. Classifications are represented in Fig. 2 and Fig. 3.

Moreover, the IECC established a morphological classification of endocervical adenocarcinoma (ECA) that is linked to aetiology, as is common in other organs, including the vulva and oropharynx. The IECC classification adds to the mentioned classification of adenocarcinoma set by WHO (Fig. 3), miscellaneous and not otherwise specified (NOS) in the HPV-independent section (Stolnicu et al., 2018).

Regarding staging of cervical cancer, all the studies included in this Dissertation concluded that early-stages (stages I – II) of cervical cancer have better prognosis, survival rate and lower recurrence rate when surgery is performed (Chen et al., 2019; Stolnicu et al., 2021). Conversely, when the cancer is on an advanced stage, between IIB and IV, the prognosis is poor.

The latest staging review carried out by FIGO (Table 1) included the Silva classification system, which stratified adenocarcinomas into three patterns (A, B, C) and categorized them based on the pattern of invasion (Stolnicu et al., 2021).

Table 1. FIGO staging of cancer of the cervix uteri (2018). From: Bhatla et al., 2019.

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤ 5 mm ^a
IA1	Measured stromal invasion ≤ 3 mm in depth
IA2	Measured stromal invasion >3 and ≤ 5 mm in depth
IB	Invasive carcinoma with measured deepest invasion >5 mm (greater than Stage IA); lesion limited to the cervix uteri with size measured by maximum tumour diameter ^b
IB1	Invasive carcinoma >5 mm depth of stromal invasion; ≤ 2 cm in greatest dimension
IB2	Invasive carcinoma >2 and ≤ 4 cm in greatest dimension
IB3	Invasive carcinoma >4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or the pelvic wall
IIA	Involvement limited to the upper two-third of the vagina without parametrial involvement
IIA1	Invasive carcinoma ≤ 4 cm in greatest dimension
IIA2	Invasive carcinoma >4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases) ^c , irrespective of tumour size and extent (with r and p notations) ^d
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent pelvic organs
IVB	Spread to distant organs

^a Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumour size and extent, in all stages. Pathological findings supersede imaging and clinical findings.

^b The involvement of vascular/lymphatic spaces should not change staging. The lateral extent of the lesion is no longer considered.

^c Isolated tumour cells do not change the stage but their presence should be recorded.

^d Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation should be Stage IIIC1r; if confirmed by pathological findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

While the majority of professionals grade endocervical adenocarcinomas using FIGO criteria for endometrial carcinoma, there is no universally accepted classification system for endocervical adenocarcinomas (Stolnicu et al., 2021).

5.3 Biomarkers

5.3.1 Biomarkers related with cervical cancer susceptibility

Biomarkers could also be classified depending on the molecule type; the following biomarkers have been identified as miRNAs and lncRNA (long non-coding): *miRNA-196a2* by itself, and *miRNA-196a2* along with *miR-146a* and *miR-499* (Thakur et al., 2019); *miRNA-17-92* (rs9588884 GG) (Huang et al., 2020); *lncRNA HULC* rs1041279 (Hepatocellular carcinoma up-regulated lnc-RNA) (Wang et al., 2020), and *CASC15* (cancer susceptibility 15) (Gao et al., 2020). Other described biomarkers are certain polymorphisms of the successive receptors: *TLR9* (Tall Like Receptor 9) and *TLR4* (Tall Like Receptor 4) (Pandey et al., 2019); *FLT1* (rs9513111) (fms-Related Receptor Tyrosine Kinase 1) (Han et al., 2019) and the deficiency of vitamin D receptor (VDR) (Phuthong et al., 2020).

In addition, polymorphisms of the sequence of protein coding genes have also been identified: *CYP1A1* (C2453A) (Cytochrome P450 family 1 subfamily A member 1) (Wongpratare et al., 2020), *TNFAIP8L1* (rs9917028, rs10426502, and rs1060555) (Tumor Necrosis Factor alpha induced protein 8 like 1) (Han et al., 2019), *TNFAIP2* (rs710100) (Tumor Necrosis Factor alpha induced protein 2) (Ainiwaer et al., 2020); *SMAD2* (rs4940086 and rs8085335) (SMAD family member 2) (Haque et al., 2020). Moreover, the following genes: *PGF* (rs2268615) (Placental Growth Factor) (Ainiwaer et al., 2020); *HLA-DQB1*03* (Major Histocompatibility Complex, Class II, DQ beta 1) and *HLA-DRB1*07* (Major Histocompatibility Complex, Class II, DR beta 1) alleles (Hu et al., 2018) also appear to play a role. Finally, specific polymorphisms in immunity components: *IL-10* rs1800872 (Interleukin-10) (Pereira et al., 2020), and *IL17A* rs3748067 (Interleukin 17A) (Niu et al., 2017) also seem to be involved in the susceptibility to suffer from a cervical cancer.

5.3.2 Biomarkers related with early diagnosis

When there are no visible cervical precancerous lesions, biomarkers linked to the early-stages of cervical cancer or to precancerous lesions are essential to prevent advanced stages of the disease; therefore, patients could be treated at an early stage and mortality of CC could decrease dramatically (Wu et al., 2017).

The components identified as biomarkers are genes, promoters, miRNA, and protein transcription factors. The detailed list is as follows: variant frequencies of *HLA-A* (Major Histocompatibility complex, class I, A) alleles (Alifu et al., 2018); *MIF* (Macrophage Migration Inhibitory Factor) promoter polymorphism (-794CATT₅₋₇) (Wu et al., 2017) and *MIF* 173 G/C (Wu et al., 2011), unscheduled expression of *miRNA-146a-5p* and *miRNA-21-5p* (Ma et al., 2019), and high expression of *NF-κB* (nuclear factor-kappa B) *p52/RelB* complex (Hua et al., 2019).

5.3.3 Biomarkers related with treatment response

Biomarkers that evaluate the treatment response are another leading field regarding the individualized treatment. These could be classified according to the component type; lncRNA *BCAR4* (breast cancer anti-estrogen resistance 4) (Burk et al., 2017); determined expression of peptides and protein coding genes: *TKT* (Transketolase), *FGA* (Fibrinogen Alpha Chain) and *APOA* (Apolipoprotein) (Chen et al., 2019); *XRCC1* (X-ray repair cross complementing 1), *APE-1* (Apurinic/apyrimidinic endodeoxyribonuclease 1) (Charles et al., 2020), *PTEN* (phosphatase and tensin homolog), *ARID1A* (AT-rich interaction domain 1A) (Burk et al., 2017) and *TNF-α* (Kushwah et al., 2020).

In addition, gene encoding enzymes and immunity components accordingly: *PDC1ILG2* (programmed cell death 1 ligand 2) (Burk et al., 2017); *CD274* (CD274 molecule), variants in *IL1-RN* (interleukin 1 receptor antagonist), *IL1-β* and *IL6* (Kushwah et al., 2020), and 13 specific anti-glycan antibodies (*AGA*) (Purohit et al., 2020). Finally, the presence or absence of certain alleles of *HLA-A* gene (Alifu et al., 2018), and *ERBB3* (erb-b2 receptor tyrosine kinase 3) receptor (Burk et al., 2017).

5.3.4 Biomarkers related with the prognosis and outcomes

Once the cancer is detected and diagnosed, prognosis can be made on the basis of useful biomarkers. The following ones have been identified and organized according to the component type; circulating plasma *miRNA-205* (Zhao et al., 2020) and *lncRNA GATA6-AS* (GATA

binding protein 6 antisense) (Zhao et al., 2020). Unusual overexpression of *hWALP* (human Wing Apart-Like) gene (Nunobiki et al., 2018); in addition, the following protein and enzyme encoded by a gene were also detected: *EXCO1* (Exocyst Complex Component 1), in particular the variant rs13117307(Łaźniak et al., 2017) and *HSD17B1* rs605059 (17 β Hydroxysteroid dehydrogenase type 1) (Lutkowska et al., 2017). And certain immunity system components: *CK19* (cytokeratin) and *CK 20* (Wei et al., 2018). Finally, the non-canonical *NF-κB p52/RelB* pathway (Hua et al., 2019) and lower concentration on serum levels of zinc and selenium (Okunade et al., 2018).

Additionally, the following biomarkers are also associated with worse disease-free survival (DFS) and overall-survival (OV): *circular RNA_0018289* (He et al., 2020); regarding the immune system components: expression of histone H3 acetyl K9 and histone H3 tri methyl K4 (Beyer et al., 2017); and, lastly, low nuclear expression of nuclear receptor corepressor (*NCoR*) (Beilner et al., 2021).

Few studies detected that variant of *ERCC1* (rs3212986) (Excision Repair 1, endonuclease non-catalytic subunit) and *GST* (glutathione S-transferase) genes (*GSTM1*, *GSTT1* and *GSTP1*) are associated with the gastrointestinal toxicity induced by anti-cancer treatment (Soares et al., 2018; Abbas et al., 2018). Another reason for the treatment to be personalised to the patient is that it could decrease toxicities, increase treatment response rates, and consequently improve DFS and OV (Soares et al., 2018), as OV is associated with tumour size, tumour stage and lymph node metastasis (Qian et al., 2017).

In contrast, the following polymorphisms of the sequence of RNA, receptors, protein coding genes and interleukin, have no association with cervical cancer: *lncRNA HULC* (rs3005167 and rs7770772)(Wang et al., 2020), *miRNA-17-92* (rs982873 and rs1813389)(Huang et al., 2020); *FLT1* rs677471 (Han et al., 2019), and *XRCC3* (rs861539)(X-ray repair cross complementing 3)(Abbas et al., 2019); *IL17A* rs2275913 (Niu et al., 2017). In addition, Okunade et al. (2018) found no evidence that copper serum concentration could be used for CC detection.

5.3.5 Innovative methods by biomarkers' combination

The research has made advances and improvements on non-invasive techniques and new methods of detection. Currently, the detection of CC could be done by means of a multi-biomarker panel, by measuring miRNA (*miRNA- 20a*, *miRNA-205*, *miRNA-218*, *miRNA-21*, *miRNA-29a*, *miRNA-200a*, *miRNA-25* and *miRNA-486-5p*) levels along with squamous cell

carcinoma antigen (SCC Ag) level in blood sample (Du et al., 2020). Likewise, a panel of four-miRNA (*miRNA-146a-5p*, *miRNA-21-5p*, *miRNA-151a-3p* and *miRNA-2110*) (Ma et al., 2019).

Not only the miRNA are useful for the developing of these methods of detection; Fernandez-Renata et al. (2017) elaborated a molecular signature comprising eight degradome-related genes (*FAM111B* (FMA111 trypsin lie peptidase B), *FAM111A* (FMA111 trypsin lie peptidase A), *CFB* (Complement Factor B), *PSMB8* (proteasome 20S subunit beta 8), *PSMB9* (proteasome 20S subunit beta 9), *CASP7*(Caspase 7), *PRSS16* (Serine protease 16) and *CD74*) through which the prediction of distal metastases risk could be determined in patients with locally advanced cervical cancer. Intriguingly, 40% of the patients develop progression or recurrence even through the conventional treatment.

In addition, a study by Kaushik et al. (2021) proposed a machine learning-based model using data of cytokine gene variants (*IL-1RN* (86bp VNTR), *IL-1 β -511 C/T*, *IL-6-597 G/A*, and *TNF- α -308 G/A*) together with socio-demographics, obstetrics, and smoking parameters; this model was found to be able to predict the vulnerability to suffering from a cervical cancer.

5.4 Diagnosis

Preventable primary methods are the screening techniques for early detection of precancerous cervical lesions (Landy, Sasieni et al., 2020) and the vaccination against HPV infection (Tan et al., 2018; Dong et al., 2019). In addition, there are significant disparities regarding CC screening for women who live in poverty, who have limited access to care, or are racial/ethnic minorities (Benard et al., 2021). For this reason and because prevalence and distribution of HPV are known to vary across different geographical regions, understanding the pattern of distribution of HPV in a given population is essential to help apprise the efficiency of HPV vaccines (Tan et al., 2018).

It is evident that the most important issue, associated with the high incidence of CC, is the lack of screening, as the absence of tumour detection leads to fatal outcome; because of that, some studies confirm that initiatives, such as entertainment education strategies, and encouragement of women to seek screening and consequently improve the prevention of cervical cancer (Lamb et al., 2018; Landy, Sasieni et al., 2020). Some lack of screening may be due to the misconceptions regarding the disease or a reluctance to a behaviour change (Lamb et al., 2018). Related to this, it has been reported that, if increasing screening coverage was

increased to 100%, just in New Mexico, the estimated potential of screening to prevent cancers could be 61% (Landy, Mathews et al., 2020).

Tapera et al. (2019) showed that the health system and its organization in LMIC present barriers to access of CC treatment and care among women; the reception of the CRT is considered the most critical barrier to obtain better patient outcomes (Park et al., 2018).

The strategy that these countries should envisage is an improvement in the organization and distribution of CC screening and treatment services. Other measures, such as strong political will and mobilization of resources both domestically and from global partners to build more capacity for screening and treatment, are needed. Finally, the capacity building of health care stakeholders to improve their knowledge is also relevant; for this reason, appropriate training programs on cervical cancer should be devised, as they are essential for prevention (Tapera et al., 2019; Getahun et al., 2019).

The conventional methods used for screening is mainly Papanicolaou test or Pap test, which consists of a sample of the surface cells from the cervix and the area around. Thus, they can be checked under a microscope and uses cervical images to identify cancerous cells and image pre-processing for risk assessment, as it may also help find other conditions, such as infection or inflammation. After a positive Pap test, a cytology or a HPV test may be done to check DNA or RNA for certain types of HPV infection (Kaushik et al., 2021; Banerjee et al., 2022).

Other methods could be monolayer cytology as ThinPrep cytological test, which is an effective method that employs liquid-based cytology, although it has less sensitivity and specificity than Pap test (Chen et al., 2012; Coste et al., 2003). Also, cervical biopsy, even though has several inherent defects, because it needs to remove a tissue sample from the cervix to be done, is still a widely used diagnostic method (Ma et al., 2019).

Duenas-Gonzalez et al. (2003) reported that more than 50% of newly diagnosed CC are locally advanced, besides the poor prognosis, which is mainly due to the low accuracy of the methods used currently (Chen et al., 2019). For this reason, main efforts are intended to produce more robust, sensitive, and specific tests in gynaecological oncology; for instance, the innovating methods of diagnosis mentioned in the biomarkers section.

5.5 Treatment

The findings related to the molecular subtypes and biomarkers of CC provide insight into the treatment of cervical cancer patients with distinct therapies, with the objective of tailoring the therapeutic strategy to the genetic traits and life habits of the patient (Burk et al., 2017; Gao et al., 2020). The standard treatment can be divided into five types: surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy. Current evidence indicates that certain type treatments, or their combination, have better outcomes and advantages compared to others. The information below describes the most used methods and the reasons why certain treatment types are preferable.

Laparoscopic radical resection (LRR) (Xu et al., 2020), and laparoscopic radical hysterectomy (LRH) (Wei et al., 2018), in comparison to open surgery and traditional abdominal radical hysterectomy (ARH), are surgical treatments that cause less stress, reduce the number of patients that develop complications, and do not delay the interval between surgery and postoperative radiation therapy. Hence, they improve the recovery and the outcomes of patients. Additionally, the findings prove that robotic-assisted radical hysterectomy and traditional laparoscopic radical hysterectomy give similar outcomes (Nie et al., 2017).

The treatment for early-stages of CC could be ARH with pelvic lymphadenectomy (Sert et al., 2021), but as a consequence of bladder dysfunction - the most common long-term complications after ARH -, the nerve-sparing radical hysterectomy (NSRH) has emerged as a reducing surgery-related dysfunctions without compromising oncological outcomes (Novackova et al., 2020). On the other hand, patients with early-stage CC and at least one high-risk factor could also be treated with iBT (intracavitary brachytherapy) together with CRT, which is proved to decrease recurrence and improve PFS (Lan et al., 2017). By contrast, for patients with localized carcinoma of the cervix that is unsuitable for radical surgery, the standard treatment consists of radical external-beam radiotherapy (EBRT) followed by iBT. While combining EBRT and BT leads to better survival than just EBRT (Purohit et al., 2020), the most important prognostic factor in patients who followed this treatment is the start of the treatment (Joseph et al., 2020).

In addition, EBRT may lead to vascular toxicity and fibrosis, rendering the vagina short and narrow (Kirchheimer et al., 2012). For the purpose of lessening the adverse effects, paying attention to the radiation dose received by the vaginal region in order to reduce vaginal radiation

injury (Wang et al., 2019) is important. Furthermore, in locally advanced CC, a higher BT dose may not be able to overcome the poor response to chemoradiation because it is also associated with a high risk of extrapelvic failure (Horne et al., 2019). Other feasible choices to treat advanced CC are the combination of adjuvant hysterectomy and radiochemotherapy (Hass et al., 2017), the blastilimab monotherapy (O'Malley et al., 2021), and concurrent cisplatin-based chemoradiotherapy, compared with definitive radiotherapy (Shrivastava et al., 2018). Moreover, pelvic exenteration represents one option for the surgical treatment of residual disease to improve patient outcomes; however, this is associated with increased morbidity and mortality (Ota et al., 2008).

Treatments like adjuvant surgery (AS) (Hass et al., 2017) and Californium-252 neutron brachytherapy with EBRT plus concurrent chemotherapy (Qian et al., 2017) offer highly effective therapeutic modality with tolerable adverse effects; consequently, these strategies improve the local control, long-term survival rates of patients and reduce the adverse side-effects. Additionally, Intensity Modulated Radiation Therapy and Image-Guided Adapted Brachytherapy (IMRT/3D-IGABT) is another treatment type that improves survival over 2D techniques, owing to evolution of radiation delivery as it improves target coverage and decreases the dose to organs at risk; therefore, it lessens the toxicity for locally advanced CC (Lin et al., 2019; Pötter et al., 2018).

Exclusively, on the occasion when deficiency of zinc, selenium or VDR has been detected on patients, which might depend on dietary and environmental factors, a treatment based on the routine provision of these trace supplements may result in reduced CC occurrence (Okunade et al., 2018; McCullough et al., 2007). Not all the combinations have successful outcomes. For example, Pignata et al. (2019) determined that the combination of cetuximab (CET), an anti-epidermal growth factor receptor, along to carboplatin (C) and paclitaxel (P), is feasible but not more effective than chemotherapy alone.

Cervical cancer patients could experience changes in their quality of life (QoL), due to treatment's adverse effects or to the effect of the cancer by itself; Li et al. (2017) confirmed that women treated with concurrent chemoradiation had more treatment-related side effects. Amongst others, these adverse effects were worse appetite loss, worse fatigue and diarrhoea, more financial difficulties, worse sexual enjoyment, and sexual/vaginal functioning, than those treated with primary surgery.

6. CONCLUSIONS

The present systematic review shows that most of cervical cancer cases could be originated by environmental factors, mostly bad lifestyle habits, together with genetic components of the patient, such as SNPs. In relation to diagnosis methods and the lack of cervical cancer screening, which is generally because the mentioned techniques are invasive and present low sensitivity, it is required to continue the research relating to new non-invasive and more sensitive methods, and to implement them on the majority of health care programs.

The classification and staging of the cancer, when the detection of the disease is already done, is one of the most deciding steps considering that these factors along with CC stage and prognosis, the treatment should be chosen and, as data indicate, tailored based on the patients' characteristics. Furthermore, genetic polymorphisms are a key element as a biomarker in cervical cancer field, as they constitute a useful and non-invasive tool which could be helpful for early diagnosis, personalising and monitoring of the treatment and estimate patients' progress.

Taking everything into account, and as it has been mentioned previously, further studies are required to make progress on diagnosis, prognosis, and treatment strategies, in addition to the identification of helpful biomarkers.

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8. PERSPECTIVA DE GÈNERE

8.1 Concepte

La igualtat de gènere es defineix com “la igualtat de drets, responsabilitat i oportunitats de les dones i els homes, i les nenes i els nens”. La igualtat no és sinònim a què les dones i els homes siguin el mateix, sinó que fa referència al fet que els drets, les responsabilitats i les oportunitats no depenguin del sexe amb el qual van néixer (Hannan, 2001).

Aquesta igualtat implica tenir en compte els interessos, les necessitats i les prioritats tant de les dones, com dels homes, reconeixent-se la diversitat dels diferents grups de dones i homes; per aquests motius és tan necessària la seva implementació en tots els àmbits de la societat.

Aplicada a l’àmbit universitari, la perspectiva de gènere o *gender mainstreaming* és una política integral per promoure la igualtat de gènere i la diversitat en la recerca, la docència i el vincle amb la societat, així com en les estructures de gestió i decisió de les universitats, tots els àmbits afectats per diferents biaixos de gènere (Verges, 2017).

Una docència amb perspectiva de gènere millora la qualitat docent i la rellevància social dels coneixements, les tecnologies i les innovacions produïdes; addicionalment, permet aprofundir en la comprensió de les necessitats, comportaments i actituds del conjunt d’una població i també contribueix a detectar el potencial desequilibri de gènere en les obres treballades (AQU, 2018).

8.2 Dades observades

Tot i que actualment la igualtat de gènere ha avançat i contínuament s'està actualitzant, per així implementar les millores, encara a les estadístiques es pot observar una clara desigualtat.

- Segons l'*Institut Europeu de la Igualtat de Gènere (IEGE)*, a Espanya l’any 2020 es va registrar que la desigualtat de gènere en termes monetaris encara persisteix; concretament, les dones guanyen el 17% menys, respecte al salari que guanyen els homes.
- Segons l'*Organització de les Nacions Unides per l’Educació, la Ciència i la Cultura (UNESCO)*, 127 milions de nenes en edat de cursar educació primària i secundària no estan escolaritzades i les dones representen 2/3 dels 750 milions d’adults, els quals els hi manquen els coneixements bàsics de l’alfabetització.

- Segons dades oficials extretes del Ministeri d’Educació, referent al curs acadèmic 2019-2020: un 55.7% de dones es van matricular en estudis de Grau, un 55.7% en estudis de Màster i un 50% en estudis de Doctorat. Són dades molt equitatives, però quan s’aprofundeix dins de l’àmbit d’estudi s’observa una clara desigualtat, ja que en els estudis de l’àmbit STEM, i específicament en informàtica, enginyeria, indústria i construcció amb un 13.4% i 29.1% de dones matriculades en estudis de Grau.

Pel que fa a la Universitat de Girona, el consell de direcció està format per: un rector, 3/9 vicerectores, una secretaria general i un gerent; així doncs, només hi ha la presència de dones en 2/4 dels càrrecs que formen el consell de direcció. Aquestes dades es poden extrapolar a la societat actual, on el gènere desenvolupa un paper tan important en l’àmbit laboral que es coneix com a segregació de gènere; els estereotips fomenten la visió on generalment els homes són més independents, competitius i segurs de si mateixos, en comparació a les dones, que se les veu més comprensives, atentes i conscients (Viladot, 2016).

En diversos estudis, s’ha observat que la percepció dels estudiants enfront de les professions també està estereotipada i respon als rols socialment assignats a dones i homes (Barberá, 2008; Mollo, 2014), aquest fet pot ser conseqüència a causa de la falta de referents de dones en llocs laborals associats a homes i viceversa; anomenat també “bretxa de gènere” en l’àmbit laboral.

Per altra banda, un context amb igualtat de gènere correspon per exemple a la situació de TechnoSperm, centre que realitza recerca, principalment centrada en la biotecnologia animal, de la Universitat de Girona, i on he dut a terme el Treball Final de Grau. Actualment, en aquest centre els percentatges de dones en els càrrecs són majors que els d’homes; hi ha un 60% de dones professors de plantilles, un 60% d’investigadores postdoctorals, un 75% d’investigadores predoctorals i un 100% de professors associades; addicionalment també hi ha més percentatge de dones redactant un Treball Final de Grau o Treball Final de Màster.

És evident, doncs, que el percentatge de dones matriculades en Graus és molt divers, segons el Ministeri d’Universitats, en el curs 2020-2021, la branca amb major igualtat va ser ciències (50.7%), per altra banda, els graus d’enginyeria i arquitectura van obtenir el menor valor, amb 25.7% dones matriculades.

Pel que respecta als articles treballats per dur a terme la revisió sistemàtica del Treball Final de Grau, els quals són 68 en total, només 27 han sigut útils per poder observar i comparar el nombre

de dones i homes que van ser partícips de les investigacions en cada article. Cal mencionar, que no és una mostra representativa a causa de la forma de citar, ja que únicament indiquen el cognom i la inicial de l'individu, i també perquè l'origen de determinats noms no permet identificar el gènere de l'individu.

Així doncs, dels 27 articles, s'han recomptat un total de 255 investigadors/es, dels quals 122 són dones i 133 homes, representant un 47.8% i un 52.2% respectivament. Sembla que hi ha certa igualtat, però no és una dada prou representativa per afirmar-ho, ni tampoc es pot extrapolar perquè segons l'Institut d'Estadística de la UNESCO, en un estudi de la presència de dones en els camps STEM (ciències, tecnologia, enginyeria i matemàtiques).

8.3 Iniciatives i plans d'actuació

Les iniciatives a escala global amb més difusió segurament són l'11 d'octubre com el Dia Internacional de la Nena, el 8 de març com el Dia Internacional de la Dona i específicament a l'àmbit que tinc més proper, el dia 11 de febrer com el Dia Internacional de la Dona i la Nena en la Ciència. Aquestes activitats fomenten la igualtat de gènere i participen en la visibilització de les dones en l'àmbit científic – tecnològic, alhora impliquen un recordatori anual per celebrar el que s'ha aconseguit i també exposar i plantejar com afrontar les limitacions que encara no s'han superat.

Actualment, a Catalunya, l'Agència de Garantia de Qualitat del Sistema Universitari Català (AQU) obliga la incorporació de la perspectiva de gènere en tots els graus i màsters de l'educació superior a Catalunya.

Addicionalment, l'article 28, apartat 1 a) de la Llei 17/2015, d'igualtat efectiva entre homes i dones, indica que “les sol·licituds d'acreditació de títols de grau i de màster hauran d'anar accompanyades d'un informe que detalli com s'ha incorporat la perspectiva de gènere en el pla d'estudi o els plans de millora previstos per a fer-ho possible” (AQU, 2019).

A continuació es destaquen alguns plans d'acció per la incorporació de la perspectiva de gènere de diverses universitats de Catalunya, juntament amb iniciatives que promouen la inclusió de les dones en els estudis STEM.

- El projecte pilot Gènere i Docència (GiD) de la Universitat Politècnica de Catalunya-BarcelonaTech (UPC), aquest projecte es va desenvolupar durant el curs 2018-2019; el seu objectiu principal consistia en la formació de personal acadèmic per dotar de les

eines adequades i així poder redefinir els cursos incorporant la perspectiva de gènere en la docència (Peña, 2020).

- Pla d'igualtat Isabel de Villena 2018-2022 de la Universitat Pompeu Fabra (UPF), concretament l'eix 2 (Universitat Pompeu Fabra, 2018), on es descriuen els propòsits per aconseguir una docència, recerca i transferència de coneixement sensibles al gènere i, per tant, s'impulsa la perspectiva de gènere en la docència.
- El document elaborat per l'Observatori per a la Igualtat: Investigació amb perspectiva de gènere, en aquest es descriuen els punts claus per la introducció de la perspectiva de gènere en el disseny i la implementació dels projectes de recerca, des de la formació dels equips, el disseny de la investigació, la difusió dels resultats i l'avaluació de l'impacte de gènere (Freixes, 2016).
- Programa STEM Talent Girl: programa impulsat per l'*Instituto Nacional de Tecnologías Educativas y de Formación del Profesorado* (INTED), es focalitza en fomentar el talent i promoure les vocacions STEM entre les dones i nenes d'Espanya.

Cal esmentar que en l'àmbit internacional, la *Commission on the Status of Women* (CSW), és el principal òrgan intergovernamental dedicat a la promoció de la igualtat de gènere i de l'apoderament de les dones (ONU Mujeres, n.d.).

També és necessari mencionar que la UNESCO va publicar: “*Del acceso al empoderamiento: estrategia de la UNESCO para la igualdad de género en y a través de la educación 2019-2025*”, document el qual explica el compromís a llarg termini a favor de la igualtat de gènere, i en els ensenyaments extrets en dècades de treball encaminat a promoure la igualtat de gènere en i a través de l'educació.

8.4 Reflexió

Amb el conjunt de dades comentades anteriorment, es pot veure la comentada “bretxa de gènere” no només en l'àmbit de l'educació, aquest concepte inclou totes aquelles diferències implícites en què un individu hagi nascut dona; són diferències i limitacions tan normalitzades i integrades en la societat que per això sovint és complicat aconseguir la igualtat. Per exemple, una clara limitació és quan una dona vol ascendir a càrrecs de responsabilitat; recollint dades de la Universitat de Girona, actualment el càrrec de rector està ocupat per un home, en tota la història només una dona ha estat ocupat el càrrec de rectora, des del 2005 fins al 2013.

Per altra banda, aquesta distinció de gènere s'introdueix des que es comença a entrar en contacte amb el sistema acadèmic i l'educació actual. Aquest apartat m'ha fet reflexionar en el nombre de referents dones que vaig tenir al llarg del meu període acadèmic, i realment no van ser tants i no només en l'àmbit científic, sinó que també a les assignatures d'història, de música o de filosofia.

A causa de la falta de referents per les nenes, ja que no es tracta d'un cas aïllat, es va formar l'associació #Nomorematildas, la qual denuncia les conseqüències de l'Efecte Matilda, en honor a Matilda Joslyn Gage, la primera activista dona que va denunciar i assenyalar la injustícia que ha ignorat, de manera sistèmica, els descobriments de científiques o que s'atorguin els mèrits i reconeixements a un home, ja sigui integrant de l'equip d'investigació o un familiar, d'un descobriment que ha fet una dona. Rosalind Franklin, Lise Meitner o Hedy Lamarr són algunes de les víctimes de l'efecte Matilda (No More Matildas, n.d.).

La falta de referents femenins té un impacte en les aspiracions professionals de les nenes, aquest fet es tradueix en una menor presència de dones matriculades en les carreres STEM. Així doncs, aquesta associació vol recuperar aquestes figures de dones referents, introduint-les com a exemples en els llibres de text, amb el mateix pes que els exemples de referents masculins, així fomentant la vocació científica en les nenes i adolescents i reduint la desigualtat.

Un factor que també influeix és la confiança i la motivació que tenen les noies en què poden aconseguir els mateixos o millors resultats que els seus companys; UNICEF determina que el 70% d'individus, en 34 països, associen més la ciència als nois que a les noies, també observen que les nenes presenten major inseguretat respecte a les seves capacitats en els camps STEM, respecte als nois (Alam, 2020); conseqüentment, un menor nombre de nenes presenta motivació i decideix estudiar algun àmbit relacionat amb la ciència, tecnologia, enginyeria o matemàtiques, i per tant, a mesura que passen les generacions les dones són una minoria en els Graus, Màsters, Doctorats i les professions relacionades amb aquest camp.

Seguint amb conceptes que representen la desigualtat, també veig necessari introduir el terme “sostre de vidre”, que representa l'exclusió de dones, capacitades a un ascens, l'assoliment dels càrrecs de més responsabilitat, els quals estan associats de manera sistèmica als homes.

Alguns dels arguments que justifiquen el “sostre de vidre” són tals com la maternitat i el doble paper de la dona com a treballadora i mare; aquests factors requereixen mesures de conciliació

en l'àmbit laboral, ocasionalment s'entén com una despesa no atribuïble a l'empresa i conseqüentment hi ha una major pressió en l'economia familiar i s'addicionen més obstacles a la dona, en comparació als homes (Pueyo, 2020).

Actualment, a Espanya, segons la *Asociación de Mujeres Investigadoras y Tecnólogas* (AMIT), només hi ha 2684 dones investigadores i tecnòlogues registrades en l'àmbit STEM. Juntament amb els arguments comentats anteriorment pel concepte “sostre de vidre”, es poden afegir el conjunt d'estereotips de gènere; aquests encasellen a les dones, i també als homes, en funció del rol assignat socialment i que es basa en el conjunt de característiques socials, culturals i psicològiques associades al gènere de l'individu.

Per tant, com que les comunitats en l'àmbit global difereixen entre elles, es pot entendre que implícitament cada societat presentarà un rol assignat a la dona específic, que pot ser diferent o no entre determinades comunitats.

Resumidament, a causa de diferents factors, com els estereotips, la falta de referents o a causa de societat, la desigualtat de gènere encara està molt present en tots els àmbits que ens envolten al dia a dia; sí que s'ha de tenir en compte el progrés que s'ha anat aconseguint, encara que aquest s'ha hagut de lluitar durant molt de temps. Com he comentat anteriorment, determinats punts de la desigualtat de gènere estan molt enterrats en la societat i en la manera de viure de cada individu, per això s'ha d'intentar identificar-la en les situacions que tenim més properes i habituals, i que es produeixen de manera inconscient. És veritat que durant el meu trajecte per la universitat, no m'he sentit en desigualtat de gènere, ja que cada any m'he trobat amb moltes més companyes que no companys; però sí que he notat una majoria d'homes que m'impartien les lliçons.

M'agradaria remarcar, que el tema de la perspectiva de gènere és molt rellevant i no s'ha de continuar implementant cada cop en més àmbits, ja que cada pas, per petit que sigui, és un assoliment aconseguit. Dels 5 anys que he cursat la carrera, aquest últim ha sigut el que més he vist la introducció de la perspectiva de gènere, en assignatures tals com Biotecnologia de la Reproducció, on la professora va decidir dedicar els últims 5 minuts de cada lliçó a presentarnos una dona important en la ciència, i també a l'assignatura de Projectes; tot i això, crec que encara es podria introduir més en cursos posteriors, per exemple amb la introducció de debats sobre la perspectiva de gènere en determinades assignatures.

Addicionalment i per acabar, penso que el seminari que se'ns va impartir, juntament amb els companys/es que també fan el Treball Final de Grau, amb l'equip de TechnoSperm i el fet d'haver d'incloure una perspectiva de gènere, afavoreixen que estiguem actualitzats amb la informació, les iniciatives i els conceptes de la perspectiva de gènere.

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