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Original Research Article

A new study biological role of hpv infection, oral contraceptive use, sex hormones and bisphenol A and increase rate cancer of cervical in libya

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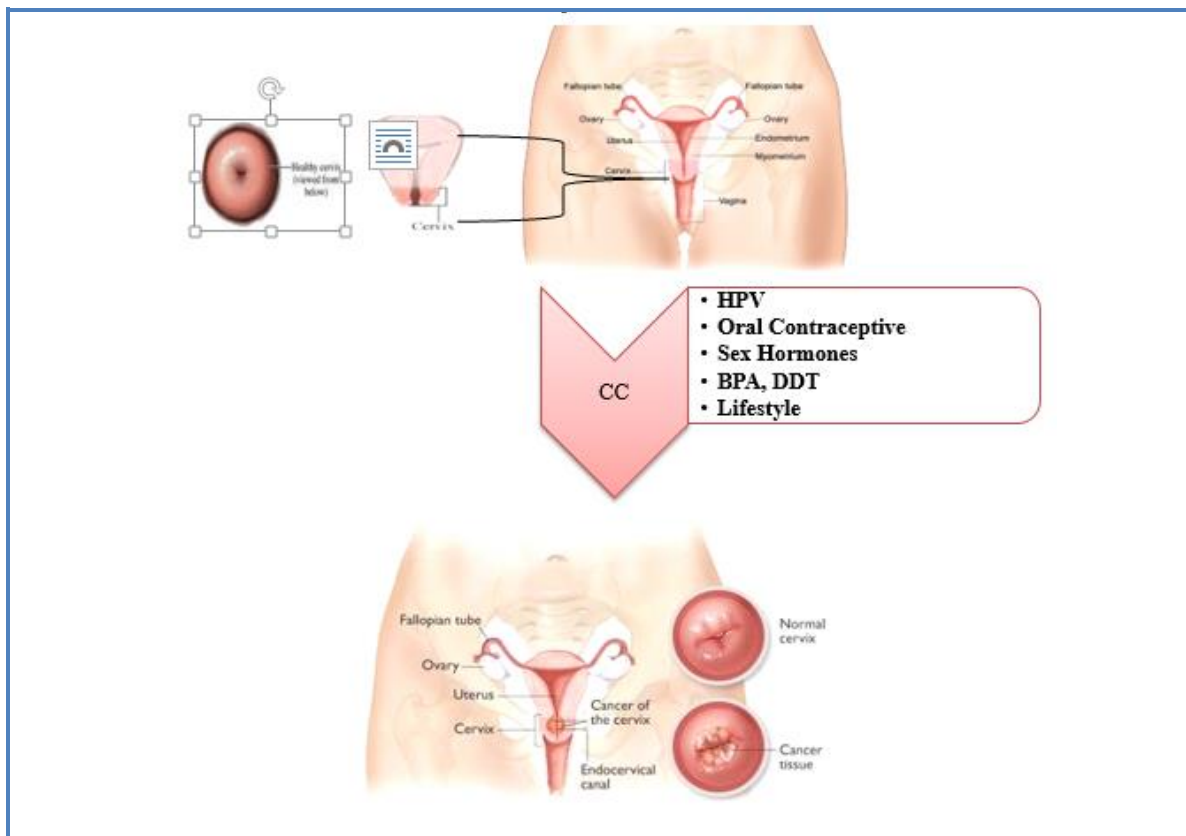
ABSTRACT

Cervical cancer (CC) has imposed a massive global burden. As yet, the first study on the causes and risk factors associated with the CC disease that conducted in Libya aimed at investigating the major cause's CC such as Human papillomavirus (HPV), oral contraceptive, sexually transmitted infections, bisphenol A and nutritional factors might also play a role is the major type, accounting for approximately 16.7% of cases in Libya. The results show the highest incidence of cervical cancer between the ages of ≥ 95 at 50%, followed by the ages between 55-65 years at 23%, while the lowest rate among women between the ages of 35-45 is 16% and 15- 25 by 11%, respectively. The increase in the infection rate is attributed to several factors as HPV and others.

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Graphical Abstract



Introduction

Cervical cancer (CC) is a huge global burden. It ranks second in the world after breast cancer. Every year, half a million women are affected worldwide, with a global death rate of about 60%, which is higher in developing countries [1]. The lack of early detection of CC and lack of awareness led to a high mortality rate among women. CC, if left untreated, will threaten the lives of many women. CC is an affects woman at the cervical region, where the uterus is attached to the vagina. CC has two main types, squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma cancer develops in the epithelial lining of the cervix, while women develop adenocarcinoma by developing it from the gland cells. It is defined as a precancerous adenocarcinoma. Since 400 B.C, the scientist Hippocrates, known as the founder of modern

medicine, described CC as an incurable disease that destroyed the uterus, always leads to death, and concluded that it should be left untreated [2]. During the 1960s, during the Industrial Revolution, a comprehensive examination was used to detect and treat precursors of cancer, resulting in the incidence rate falling to half the previous levels [3]. During the 1930s and 1940's, scientists Hinselmann and Papanicolau explored methods of screening and treating CC. The invention of the colposcope by the scientist Hinselmann revealed precursor lesions in the uterus (portio epithelium and cervix uteri), the targets biopsies and microscopy. Moreover, a weak acetic acid solution of 8 to 16 times is used during a cervical enlargement procedure using a colposcope, that a routine examination of women through the entrance and lower part of the cervical canal from outside the vagina [4].

Vaginal cytology is known as a Papanicolaou smear (Pap smear) [5], and the name is due to the scientist Papanicolaou, which a natural epithelium, precursors and invasive cancer were identified after cleaning the cervix and examining a smear under a microscope. In 2008, the scientist Zur Hausen [6] won the Nobel Prize for his discovery that the human papillomavirus (HPVs) is the main factor in the development of CC, as he needed to convince the international community 20 years what he reached during the seventies. Moreover, HPV contains more than a hundred types, with fifteen being considered high-risk types that specifically affect women in the cervical region [7]. The most studied common candidate agents are Pap, OCs, BA and female sex steroid hormones cause the development of cervical cancer in sites of normal epithelial cells (called cervical intraepithelial neoplasia (CIN)) rather than invasive cancer [8, 9]. Endocrine chemicals are environmental compounds (natural or synthetic), which impair the function of the endocrine system which leads to harmful health outcomes. The highly heterogeneous endocrine disruption is triggered by the many synthetic chemicals used in agriculture and industry as well as many consumer products. Other most common industrial chemicals cause CC such as Fungicides (vincllozolin), dioxins, polychlorinated biphenyls (PCBs), polybrominated diethyl ethers (PBDEs), plasticizers [bisphenol A (BPA) and phthalates], herbicides, and pesticides [methoxychlor, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT)] [10]. Moreover, the endocrine system (phytoestrogens) can be inactivated by plant-derived substances [11]. EDCs are weakened by the presence of many different mechanisms for endocrine system functions [12], Estrogen receptors (ERs) or altering estrogen signal pathways have harmful effects when they interact with them [13]. Breast, uterine, ovarian

and CC are among the tumors that affect female sex. Estrogen hormone is a first to cause malignant tumors, so when exposed to a prolonged period or large doses of exaggerated estrogen; it causes the growth of malignant tumors such as CC and others [14]. It is still debatable if ovarian cancer is estrogen dependent, whereas CC is mostly due to infection with oncogenic viruses [the human papilloma virus (HPV)] [15]. The cervix is an estrogens-responsive tissue. There is a very sensitive to stimulating steroid hormone in an ectocervix of uterine, which acts as a site to start the formation of cancerous tumors [16]. A hormonal steroid contraceptives and frequent full pregnancy used closely was related to infection with HPV and an increased risk of CC [17, 18]. Studies confirm that the presence of HPV infection does not necessarily lead to the development of CC. Therefore, the presence of additional synergistic factors such as estrogen stimulates the carcinogenicity associated with the presence of HPV [19]. In this work, we discuss the vital role of sex hormones, endocrine disrupting chemicals (EDCs), and oral contraceptive usage in CC.

Methods

This is a descriptive comparative study using nationally representative data from 2014 to 2019; Ethics committee was not required. Data within this work was predominantly sourced from the National Hospital, and also in this report, Twitter and Facebook post is used to recruit participants and spread information; and also used short a questionnaire verified sexual behavior. The study was based on the 6-year age groups, from 15 to 95 years old, with CC. On the basis Classification Diseases of the International data were selected. The following stages were studied: (1) age and gender determined; (2) deaths had occurred abroad; (3) <20 and >85 years old. A total registered from

CC 2014 to 2019 was 4760 and 6874, respectively, and the proportion of studied cases was 10.3% and 20%, respectively. Since this investigation used data by sources of secondary available in a domain of public which do not identify sample members, it was not necessary to obtain ethical approval. In addition, the medical records that did not contain all the necessary information for the study were excluded. We expect women with CC to be much higher than the statistic declared for several reasons, for example there are cases that have not been recorded in medical records and that are often transferred outside Libya for treatment.

Results and Discussion

In general, the health and life of a Libyan woman at the age of less than 39 is at an increased risk of developing CC, which accounts for a death rate of up to a third of deaths at a very early age. In fact, the mortality rate increases among younger age groups, unlike

chronic and other diseases. This requires the development of an effective strategic plan to ensure adequate detection and treatment for the patient. The main objective of this report is to educate Libyan women in particular that CC can be prevented and cured, if detected early. Although data showed that CC was increased considerably from 2014 to 2019. There are many problems and obstacles facing Libyan women that prevent them from obtaining health care in a timely manner, abuse by health professionals, lack of culture and lack of healthcare services. Moreover, access to health centers is difficult due to the geographical distance. Also, lack of early diagnosis, lack of media and professional awareness among workers at the Ministry of Health is one of the reasons for the spread of CC rates. Experimental analysis allows us to know the causes of CC from another angle in Libyan women. Moreover, the reasons are for the standardized classification of CC, to allow calculations more in line with reality.

Table 1. Epidemiological studies eligible is for this review of the relation between HPV positivity and use of oral contraceptives, bisphenol A, sex steroid hormones, and multiparity (Sexual partners)

Age	HPV type High-risk	% HPV positive in study	Relative risk adjusted for				OCs
			Sexual partners	BPA, DDT	Sex steroid	Nutritional factors	
15-25	High-risk 16, 18	11%	Yes	Yes	Yes	Yes	Yes
35-45	High-risk 16	16%	Yes	Yes	Yes	Yes	Yes
55-65	High-risk 16	23%	Yes	Yes	Yes	Yes	Yes
≥ 95	High-risk 16	50%	Yes	Yes	Yes	Yes	Yes

Early diagnosis is a key survivorship. Combining regular screenings with patient during process of diagnostic help improve outcomes across the Libya in any setting that must provide CC screenings. The evidence from observational study has consistently found a relationship between HPV and other sexually transmitted infections, particularly Chlamydia trachomatis; in addition, it had linked with

increased risk CC (Figure 1a, b). In this respect, screening and sexual and reproductive practices linked with increase rate CC in Libya. Similarly, oral contraception has been linked with increases risk CC (95%) and response analyses have shown higher risks with longer durations of use. However, the available data reveal correlation between contraceptive prevalence uses among women aged 15–49

incidences CC. The oral contraception prevalence causes incidence increase rate of CC

for the period 2014–2019 in Libya (Table 1 and 4).

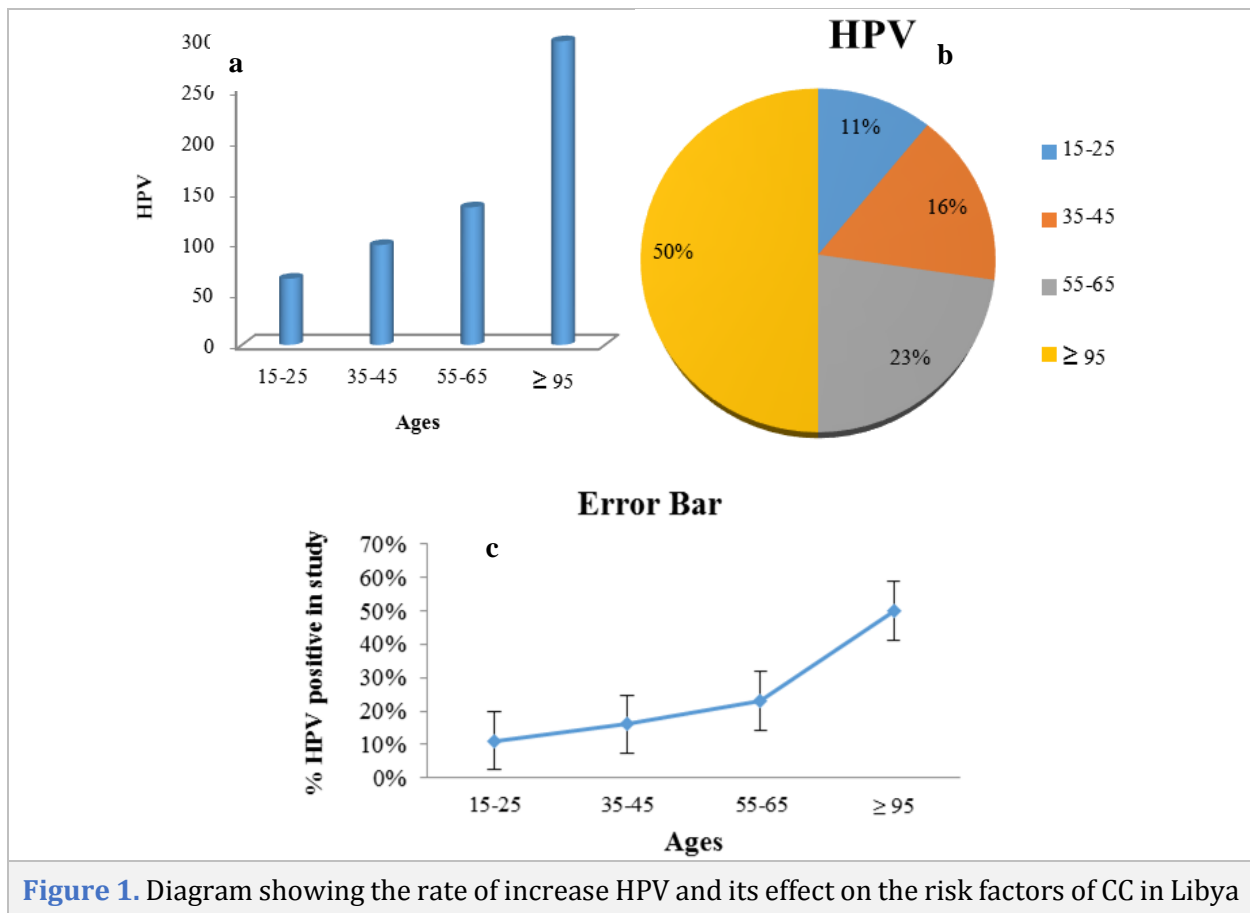


Figure 1a and b show the highest incidence of CC among women aged 65 and ≥95 by 50%, followed by women between the ages of 55-65 by 23%, while the lowest incidence among ages 35-45 is 16% and 15-25 by 11%. The results in Figures 1a and b show that the incidence of cervical cancer increases with age, and women are at risk of developing cervical cancer early from the age of 15 to 35 years, so we are working to educate women and encourage them to an early examination and treatment to protect them. The increase in the incidence rate among young ages groups are attributed to the lack of diagnosis and early examination for

these ages groups ranging from 15 to 95, as well as the lack of HPV vaccinations 16 and 18; and also bad dietary habits. The rate increased CC between the young and the elderly. Figure 1c error bar can only be used for comparison between age groups and the similarity between Figures 1a and b, it shows a small error bars when compared with the increased incidence of cervical cancer and HPV 16 and 18. The error rate appears approximately 1%, as the chart shows a gradual increase from 15 to 45, the difference between them is 5%, while between 45 to 65 is 7%, and the difference between 65 to 95 is 27%.

Table 2. Compare treatment of CC in and outside Libya

Type	Accessibility to medical treatment		Accessibility to radiotherapy		Vaccines	
	In Libya	Outside Libya	In Libya	Outside Libya	In Libya	Outside Libya
Surgery for early stage disease	Very rare	-	NO	-	Very rare	-
Surgery for late stage disease	Yes	Yes	Yes	Yes	Yes	Yes
Diagnosed at early stage	NO	-	NO	-	NO	-
Undiagnosed at early stage	Yes	-	Yes	Yes	Yes	Yes
Standard of care	Low	High	NO	High	NO	High
Options to cure	Few (Hysterectomy)	Many	NO	Yes	NO	Yes
Health centers	NO	Yes	Yes	Yes	NO	Yes
Level of education	Low	Yes	NO	OK	Few	Yes

Table 3. Cervical Cancer Screening and Diagnostics

Type	Program performance indicator	Centers for Disease Control (CDC) Standard	Libya
Screening	initial program Pap tests	≤7	Yes
	Rarely	≥60	Yes
	Never screened	80	Yes
	Age at Diagnosis ≥ 15	≥85	Yes
Cervical Cancer Diagnostics (CD)	Abnormal screening resulting with complete follow up	Not found	Yes
CD	Abnormal screening resulting: time from screening to diagnosis >90 days	≤1	Yes
CD	Invasive carcinoma, time from diagnosis to treatment > 60 days	Not found	Yes
System Food (SF)	Healthy	<35	Yes
System Food (SF)	Bad diet	>70	Yes

Table 4. Pap test according to age group

Ages (y)	2014-2019	2014	2015	2016	2017	2018	2019
15-25	0.17	1	-	-	-	-	-
25-35	0.50	-	-	-	2	1	0
35-45	1.83	3	4	1	4	1	0
45-55	5.17	5	4	2	2	11	5
55-65	5.00	6	6	6	9	2	3
≤ 95	8.83	8	9	10	10	11	5

In this work, we recommend a comprehensive CC scan for women aged 15–95 years. Women over the age of 15 need routine screening to ensure their safety (Table 2, 3). Moreover, the incidence of CC increased among young girls and the rate continued to climb until the age of ≥ 45 years. With an advancing age of women between the ages of 15–65, the percentage has increased recently for unchecked cases. With an advancing age of women between the ages of 15–65, the percentage has increased recently for unchecked cases. To prevent CC cases and deaths between older women and young adults, we need to make more efforts to reach women

who are not screened, whose ages range from less than 20 years. In Libya, all cases are treated with complete hysterectomy. Due to the lack of health center is for treatment, awareness, lack of expertise and qualifications of medical cadres. For young women than 40 aged, 1% CC cases diagnosed in aged 15–39, 1% of women were diagnosing 20–29 aged, and the women 0.17% is diagnosing younger than 20 aged (Table 4 and 3). Cases averages 5,066 CC annually from 2014–2019, with average of cancers 16.7 year of per (rate of females 0.15 per 100,000) among these aged 15–19, and 122 cancers per year (rate of females 1.4 per 100,000) among these aged 20–24 (Table 5).

Table 5. A National Cancer Registry Program 2014–2019 and the annual average census of CC

Ages (y)	Average annual number of CC	Estimated number of Pap smear examinations	The number of Pap tests performed for each cancer diagnosed
15-25	285	2	570
25-35	291	2	582
35-45	636	11	1128
45-55	1363	4	2726
55-65	1504	7	3008
≥ 65	1128	3	2256

This is first study conducted in Libya that report high CC. CC is the commonest cause of cancer morbidity and mortality among Libyan women. Therefore, a standard of age rate is estimated at 16.7/100,000 per year. High-risk HPV infection is a necessary cause. High-risk HPV is sexually transmitted with a strong association existing between sexual activity and CC risk. Only a small proportion of high-risk HPV infected women go on to develop squamous intraepithelial lesions or invasive cancer. Thus, there should be common factors for HPV infection that lead to the development of CC. There is scant information on sexual activity in adult Libya women, despite high persistent levels of high-risk HPV among older women. It is known that the cervix is greatly affected by hormones such as specially estrogen,

which controls migration, malignancies, proliferation, apoptosis, and others. The association of estrogen hormone with oral contraceptives (OCs) increases the risk of infections in CC in hormone-responsive tissues, which causes cancers such as cancer of the cervix, vagina, ovaries, breasts and others. A correlation between synergistic mixture and high risk HPV infection is as a stronger cancer agent due to estrogen shifts than involving a non-physiological process (Table 1). By transcription viral gene products, and subsequent integration of genomic assimilation of high-risk HPV into the host genome, the HPV infection begins successfully in cancer in a cyclic dependent form of the HPV. Defense systems classified as viral oncogenes as p53 and Rb when linked to carcinogenic proteins such as E₆

and E₇. The viral mechanism encourages hormones that affect cloned cells, such as the estrogen hormone, which induces CC. The estrogen hormone plays an important role in promoting the infection of HPV, which stimulates the increase in the incidence of CC. Moreover, Oral contraceptives use led Long-term to increase risk developing CC. This study supports the relationship between using pills for a period of 5 years or more, and slightly increasing the risk CC. This study conducted in Libya concluded that the increased risk CC was the result of long-term use of OCs, which may be a consequence of the non-detection of HPV infection. There is a strong correlation between OCs and sexually transmitted HPV and an increase in the incidence and mortality of CC among Libyan women with genital infection. An annual cervical test is also suggested to detect any cervical changes for pill users. Also, there is a close relationship between women infected with HPV and an increased incidence of CC as a result of repeated pregnancy (multiple pregnancies), as well as repeated miscarriages. Results from survey of the Libya aged 15–95 years observed a cervical HPV prevalence of 16.7%. In addition, among the most prevalent types is being HPV16 infection. Therefore, we expect a significant increase and a higher incidence CC in the future. As a result of awareness lack and culture are in Libyan. Absolute risk, not relative risk, is more important from a public health point of view. Women with tumors inside the epithelium of the cervix must undergo regular examination. Libya did not ban chemicals containing BPA, DDT, and did not develop any management plan. The Libyan Health Organization has also not warned or prevented the entry of these carcinogenic substances. The citizen has not been educated about the dangers of this and other material. In this study, we have issued warnings due to direct link between dose and

incidence. In general, society and the Ministry of Health and Education of Libyan have not yet realized the health risks posed by the biotoxic nature of BPA, DDT and also dietary patterns (Table 1). The Western diet and traditional Libyan food was distinctive by eating large amounts of red meat, chips, and others, lower consuming olive oil. There is also a close relationship between the health effects associated with eating habits and the increased mortality and cancer incidence. For this, the risk of developing CC associated with HPV and an unhealthy diet. Although there are several factors that trigger HPV infection, such as lifestyle, diet, social and economic factors. Evidence indicates that behaviors of sexual such as early sexual intercourse, many sexual partners, and long-term use of OCs are among the most basic foundations of a relationship between HPV infection and the risk of CC in Libya. Thus, Factors that affect sexual activity and behavior must be taken into account, as well as most urgently needed to investigate the relationship between HPV risk and C and dietary patterns. We suggest several nutritional intervention programs are reducing the incidence of cancer and improving health care and quality of life; as evidence is growing on the relationship of dietary patterns to increasing the incidence of female cancers in Libya. Moreover, this is the first study to assess the relationship between diet, HPV, CC and CIN risk high-grade nationwide. CIN tumor can not be predicted, and pathological examination cannot distinguish lesions; currently, most CIN lesions are treated with surgery by removing the affected and damaged part, which results in to continued treatment and complications for the patients. In Libya, CC is now treated using the complete surgical excision of the uterus (hysterectomy) (Table 2). This procedure has complications from several aspects, including psychological. Consequently, a substantial

number of women will remain exposed to potential side effects treatment of surgical CC.

Conclusion

Human papillomavirus is one of the most important causes associated with CC, especially HPV 16, which accounts for half of all high-risk CC cases. CC represents a major burden on the Libyan state, as it ranks second in terms of prevalence nationwide, at a rate of 16.7%; the reasons for the high rates of death and infection with this cancer are due to lack of early detection, lack of awareness of effective prevention methods, and the state's inability to provide vaccines to treat, combat and limit the spread of cancer. Also, the continued use of OCs increased the risk of CC, recurrent pregnancy (multiple pregnancy), recurrent miscarriage, sexual partners, sexual activity, and the estrogen hormone associated with HPV are among the most important factors and causes of increased incidence of CC. In addition, a healthy lifestyle and the use of environmentally friendly materials can play an important role in preventing CC.

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Conflict of interest

We have no conflicts of interest to disclose.

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