ORIGINAL ARTICLE

Exploring risk factors and survival rates in invasive cervical carcinoma: New perspectives

Exploration des facteurs de risque et des taux de survie dans le carcinome invasif du col utérin : Nouvelles perspectives

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Abstract

Introduction: Cervical cancer is a public health issue in Algeria, it ranks at second position among female cancers.
Aim: This study sought to identify risk factors for cervical cancer and to determine their impact on patient survival
Methods: This is a retrospective study on 200 patients diagnosed during a 3-years period between January 1, 2016 and December 31, 2018. This study investigated cervical cancer risk factors and survival outcomes associations. The analysis was made by Chi Square test. The progression-free survival rate was estimated using the Kaplan–Meier method.
Results: Our study revealed that squamous cell carcinoma was the most frequent diagnosis (69.9%), it also points to early sexual activity as a significant associated risk factor (P=0.05). This finding contrasts with the relatively small proportion of cases (12.12%) linked to hereditary causes. Patients with adenocarcinoma had a lower progression-free survival (PFS) (Log-Rank test P = 0.04). Poorer PFS was associated with earlier FIGO stages (Breslow: P =0.04; Tarone-Ware: P =0.04). Age at first sexual encounter and parity, however, did not significantly predict PFS. PFS was substantially better in T1-T2 pathological stages (P = 0.000).
Conclusion: The prognosis depends on knowing these risk factors. Understanding these characteristics is crucial for improved therapy and results. We provide an up-to-date insight of current cervical cancer risk factors in oran city. These results highlight how crucial it is to comprehend risk variables and how they affect the prognosis of cervical cancer.

Key words: Cervix, cancer, risk factors, progression-free survival, Algeria

Résumé

Introduction : Le cancer du col de l'utérus est un problème de santé publique en Algérie, il occupe la deuxième position parmi les cancers féminins.
Objectif : Cette étude vise à identifier les facteurs de risque du cancer du col de l'utérus et à déterminer leur impact sur la survie des patientes.
Méthodes: c'est une étude rétrospective sur 200 patientes diagnostiquées entre le 1er janvier 2016 et le 31 décembre 2018. Cette étude examine les facteurs de risque et les associations avec les résultats de survie. L'analyse a été réalisée par le test du Chi carré. Le taux de survie sans progression a été estimé en utilisant la méthode de Kaplan-Meier.
Résultats: La plupart (69,9 %) des cas étaient diagnostiqués avec un carcinome squameux. L'activité sexuelle précoce et le développement du carcinome à cellules squameuses étaient associés (P = 0,05). Les patientes atteintes d'adénocarcinome avaient une survie sans progression (PFS) inférieure (Log Rank P = 0,04). Une PFS plus médiocre était associée à des stades FIGO plus précoces (Breslow : P =0,04 ; Tarone-Ware : P =0,04). L'âge au premier rapport sexuel et la parité, ne prédisaient pas significativement la PFS. La PFS était meilleure dans les stades pathologiques T1-T2 (P = 0,000).
Conclusion: Nous fournissons un aperçu actualisé des facteurs de risque actuels du cancer du col de l'utérus. Le pronostic dépend de la connaissance de ces facteurs de risque. Comprendre ces caractéristiques est crucial pour améliorer la thérapie et ses résultats.

Mots clés: Col de l'utérus, cancer, facteurs de risque, survie sans progression, Algérie

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What is known:

1.HPV as the main risk factor: The scientific literature is very clear about the central role of human papillomavirus (HPV) in the development of cervical cancer

2. Age at first sexual intercourse and parity as risk factors: These two factors are regularly cited as being associated with an increased risk of cervical cancer

3. The importance of stage at diagnosis: The earlier cancer is diagnosed, the better the prognosis.

What this article adds:

1. Focus on the Algerian population: The study specifically examines an Algerian population, allowing for a more refined understanding of risk factors and survival profiles in a particular geographical and cultural context.

2. Association between early sexual activity and squamous carcinoma: While the association between early sexual activity and cervical cancer is known, this study provides additional evidence showing a more specific association with squamous carcinoma.

3. Impact of histological type on survival: The study highlights the importance of histological type (adenocarcinoma vs. squamous carcinoma) on patient survival.

4. Updating data for the Oran region: The study provides recent data specific to the Oran region, which can help guide public health policies and local clinical practices.

Introduction

BCervical cancer ranks fourth among cancers in women in terms of new cases in 2022 with an incidence of 6.8 and a mortality of 8.1 per 100,000[1]. In Algeria cervical cancer ranks at the second most common gynecological cancers with the occurrence of 7.9 per 100,000 women, in terms of mortality it ranks at the fourth position with 4.5 per 100,000 women.[2]

The natural course of cervical cancer was altered by the finding that human papillomavirus (HPV) infection is the cause of tumor formation [3]. According to Zur Hausen et al[4], numerous other factors may influence the development of tumors. Cervical cancer is a multifactorial illness that presents real danger to women worldwide. It was discovered that having transmitted disease [5,6], being married young [7,8], and starting sexual activity at an early age [9,10, 11]— These are indicators of developing nations, including Africa— could be causes for developing cancer of cervix. It was proposed that using oral contraceptives, smoking, high parity, and early sexual beginning age are important factors that influence how an HPV infection affects cancer [11]. The progression of the illness may also be influenced by the subject's immunological condition [12] and the characteristics of the HPV infection, such as type, viral load, genetic variations, and DNA integration [13]. In several nations, other variables have been identified as indicators of women at high risk of cervical cancer, which may point to particular areas in need of preventive measures. Poor cleanliness, has been associated to cervical cancer in China and Africa. [14,15] High-risk HPV infection and elevated viral load [13]are linked to poorer cervical cancer outcomes, as is HPV DNA integration .[16]Immunosuppression, notably in HIV patients, accelerates disease progression and worsens treatment response.[17] Furthermore, limited access to screening and healthcare due to socioeconomic factors negatively impacts survival.[18] Given these, our work aims to further elucidate these relationships by investigating the specific links between various known and potential risk factors and the survival outcomes observed in our cohort of patients with squamous cell carcinoma and/or adenocarcinoma of the cervix. Understanding these associations within our specific patient population and across the two main histological subtypes is crucial for tailoring preventive and therapeutic strategies.

Methods

This was a retrospective, cross-sectional observational study carried out on women diagnosed with cancer of the cervix at the Obstetrical Gynaecology Department of Oran City hospital establishment in Algeria from January 1st, 2016 to December 31st, 2018. The data were collected from the patient's records with full respect for the confidentiality of the data and patients.

Tumor stage was subdivided into surgico pathological tumor stage based on the TNM (tumor-node-metastasis) 8th edition, 2017 and on the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system [19], which separated patients into two groups: early clinical stages (FIGO IA, IB1 and IIA1), advanced clinical stages (IB2, IIA2, IIB, III, IVA and IVB). The description, processing, and analysis of statistical data were performed by SPSS version 20.0 for Windows (SPSS Inc., Chicago, USA), with a significance level set at greater than 0.05.

Moreover, the data were presented in rates and cross-tabulations. The findings were presented as frequencies, means, and standard deviations. A Pearson's chi-square test ($\chi 2$) was used to evaluate associations between cervical cancer risks factors and the histological types of the correspondant disease. The progression-free survival (PFS) was the time of diagnosis until the clinically-proven progression or when censored at the latest date of the consultation. Log-rank test (Mantel-Cox), Breslow (generalized Wilcoxon) and Tarone-Ware tests were used to compare the distribution of survival data between groups. The reference values for the comparison between age of first sexual activity groups were made calculating the hazard ratio (HR) and the associated 95% confidence interval (CI).

Results

A total of 200 patients were identified with cervical carcinoma, the year 2016 recorded the highest number of cases, accounting for 40% of the total, the years 2017 and 2018 followed respectively, demonstrating a significant trend during this period. The median age was 57.21±12.95 (range: 24-93 years). We have noticed that this pathology affects women under 50 years old in 28.28% of cases (Figure 1). All medical features are represented in Table 1.

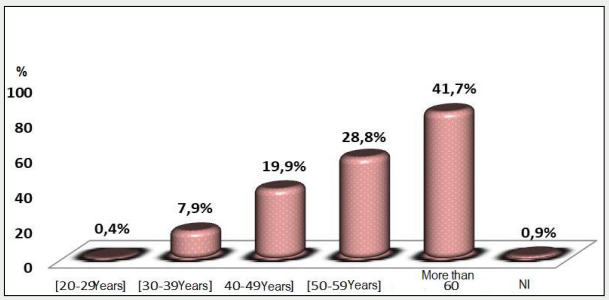

Figure 1. Distribution of patients presenting cervical cancer by age groups
NI : Not Identified

Table 1. Gynecological and clinical characteristics of patients with cancer of the cervix

Variables	Number (%)
Median age ±SD	57.21±12.95
Symptoms	
Post-coital bleeding	7(3.72)
Abnormal vaginal bleeding	137 (72.87)
Cervical polypoid mass	4(2.12)
Cervical cancer screening	3(1.59)
Pelvic pain	15(8)
Leucorrhoea	11(5.85)
Others	11(5.85)
Histology	
Types of carcinoma	
Squamous cell carcinoma	137(69.90)
Adenocarcinoma	21(10.72)
Others	38(19.38)
Types of sarcoma	
Embryonal rhabdomyosarcoma	1(0.50)
Endometrial stromal sarcoma	0
Others	1 (0.50)
Tumor size	
<20mm	13(8.85)
20-40 mm	61 (41.50)
>40mm	73(49.65)
Age of first sexual activity	
12-20 years	140(78.22)
21-35 years	39(21.78)
History family	
Yes	24(12.12)
No	174(87.88)

The used classification is the FIGO, it gives us the follow results: stage IA (1.44%), stage IB (14.49%), stage IIA (12.31%), stage IIB (30.43%), stage IIIA (9.42%), stage IIIB (18.11%), stage IV (13.76%). There were no significant differences between the carcinomatous histological types of cancer of the cervix and the two clinical parameters, menarche and parity except for the age of sexual intercourse (Table 2). From Table 3, we note that the highest risk of cervical cancer is among patients who initiate sexual activity from 21 years old with a value of OR 1.965 (95% CI= 3.66 , 1.05), meaning the probability of malignant cervical tumor is 1.96 times greater among these patients than those who experienced it earlier than this age, but when it comes to compare the relation of this variable with the histological types we have found a significant association between women initiating sexual activity at an early age and the histopathological type of squamous cell carcinoma development with P value =0.05 (Table 2).

Table 2. Association between cervical cancer risks factors and the histological types of the correspondant disease

	Adenocarcinoma Number(%)	Squamous cell carcinoma Number (%)	P-value
Age sexual initiation			
13-20	11 (57.9%)	99 (78.6%)	**0.050**
21-35	8 (42.1%)	27(21.4%)	
Menarche			
11-12	4 (20%)	38 (27.1%)	0.497
13-21	16 (80%)	102 (72.9%)	
Parity			
0-4	10 (55.6%)	51 (41.1%)	0.248
5-13	8 (44.4%)	73 (58.9%)	

Table 3. Results of multivariate tests on sexual practices and Cervical carcinomas types

Age of sexual initiation	OR	CI 95%	
		Upper	Lower
13-20	**0.737**	**0.497**	**1.093**
21-35	**1.965**	**1.052**	**3.668**

Through the creation of progression-free survival (PFS) Kaplan-Meier curves, we found that patients presenting adenocarcinoma histological type had significantly worse PFS (Log Rank P = 0.04) in comparison to individuals treated for carcinoma with squamous cells (Figure. 2 A). Interestingly, our findings indicated that early FIGO stages group had worse PFS (Breslow: P = 0.04, Tarone- Ware : P= 0.04) compared to the advanced stages (Figure. 2 B). Moreover, women with T1-T2 pathological stages (pT stages) from the TNM classification showed significantly better PFS (P = 0.000) compared to those with T3-T4 stages (Figure 2.E). As presented in Figure 2 .C and Figure 2. D, Kaplan-Meier curves of progression-free survival (PFS) suggested that parity and age of initial sexual intercourse were not significant indicators for PFS (P > 0.05 for both).

Discussion

In order to assess the incidence and prognosis of cervix carcinoma in Algeria, we carried out a retrospective analysis. Numerous predictive factors have been found to affect the rate survical of cervical cancer; some are patient-specific (e.g., age, anemia rate), additional factors relevant to the tumor (stage, size, involvement of lymph nodes, histology), and lastly additional factors associated with the characteristics of the treatment (spreading, irradiation strategy). [20]
Studies showed that the survival rate of younger patients differed from that of older patients. [21] However, data from other authors as well, especially those who examined the surgical treatment of cervical tumors, proved that age was not the prognostic factor that worsened survival. [22] The debate was clarified by the fact that young women with small tumors benefited from surgery, whereas equal aged women with large tumors received radiotherapy treatment. [23] The predictive utility of cervical tumor histology on survival has been hotly contested. Our series' low incidence

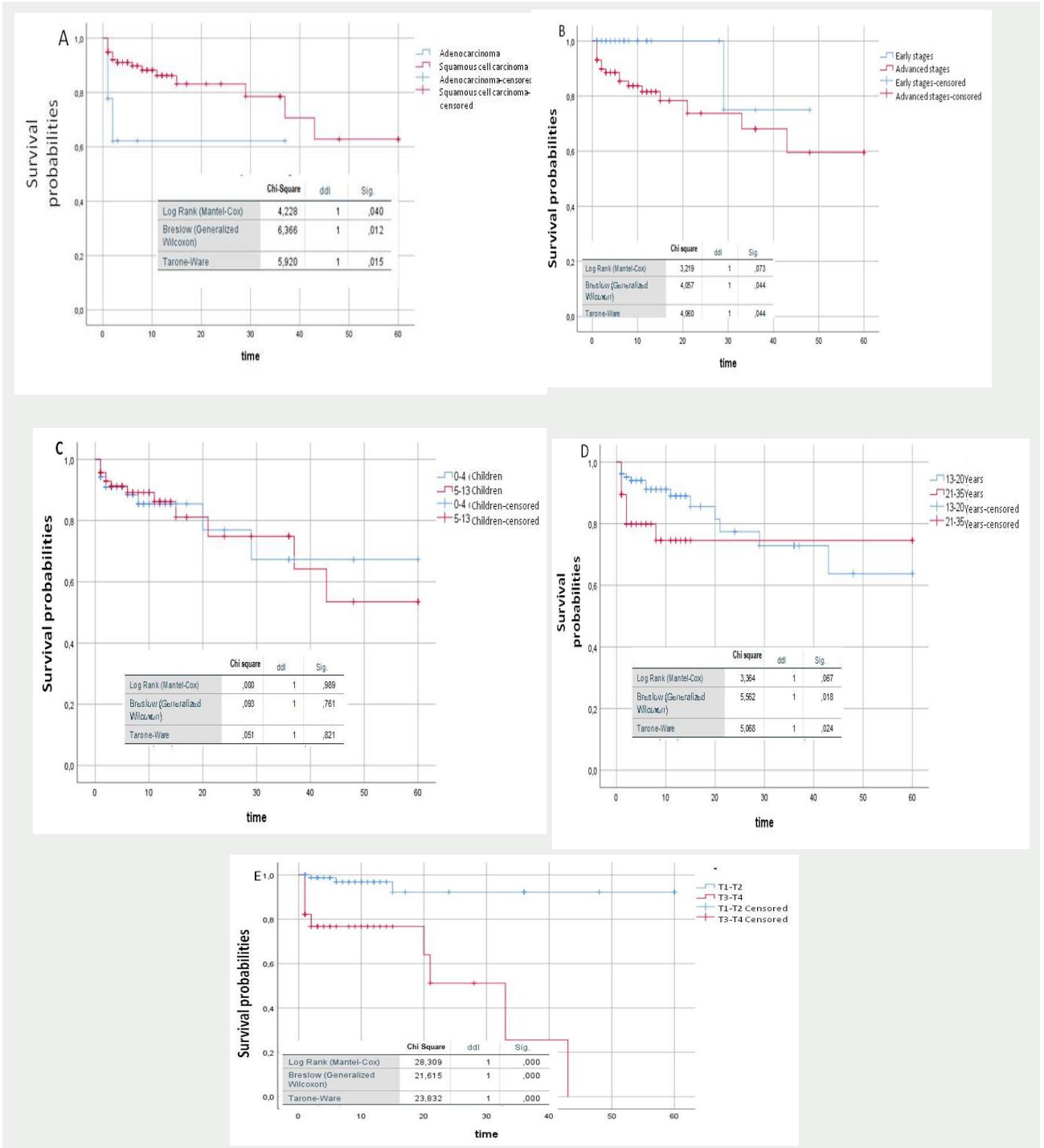

Figure 2. Kaplan-Meier curves of Progression-free survival in patients with cancer of the cervix. **(A)** : Cervical carcinoma types; **(B)** : FIGO Tumor stages; **(C)** : Parity; **(D)** : Age of initial sexual intercourse; **(E)** :T stages (from TNM staging system)

Consequently, poor prognosis among the young patients could have been resulted from variables other than age, like the tumor size (stages), age at first sexual intercourse and/or parity.

The FIGO staging is the most significant predictor of patient outcome with cervical cancer. Numerous additional established predictors are based on this classification, which is primarily determined by physical examination, and can occasionally result in under-staging[19]. In our series, there appears to be no relationship between this prognostic indicator and progression-free survival and the outcome between early and advanced FIGO staging seems to be identical. Assessment of the surgico pathological tumor size of the TNM staging system is relevant as it has the potential to change treatment decisions, our study highlights a strong association with patient's cervical cancer outcome ($p<0.000$). According to the study's findings, cancer stage is not a reliable predictor of prognosis for cervical cancer, confirming that the FIGO stage by itself is not a reliable way to make this determination, additional variables including tumor size and the probability of lymph node metastases should be taken into consideration.

A recent study revealed that adenocarcinomas were more aggressive and were linked to a lower survival rate in both early and advanced stages.

of adenocarcinomas likely explains why histology does not appear to affect progression-free survival.

Elevated risk of cancer of cervix among women with high parity is believed to be linked with a high rate of cervical abnormalities during pregnancy[24,25] and several research indicates that vaginal parity makes local changes to cervical cells due to traumas during birth. [26] A review study helps to ascertain risks of this pathology among women with high parity compared to those with low parity. [27] Indeed this meta-analysis has demonstrated that women with high parity had 2.65 times higher risks of cervical cancer compared to their counterparts (odds ratio = 2.65, 95% confidence interval = 2.08–3.38, $p < 0.001$).

According to our research, the age at which a person had her first sexual experience appears to be closely related to cancer of cervix. In fact, based to Drolet et al[28], it depends on the number of sexual partners, early sexual activity, a history of sexually transmitted infections (STDs), and frequent sex with a partner who has a history of STDs are causes for HPV infection. It has been reported that 30% precancerous lesions were observed in women having their first sexual experience between the ages of eleven and fifteen. [29]

Conclusion

Our study clearly demonstrates the importance of identifying risk factors for cancer of the cervix, particularly the role of early sexual activity and histological types in predicting survival outcomes. In the context of cervical cancer in Algeria, the findings provide insightful information that might influence targeted strategies and preventive actions.

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