# Development and Internal Validation of a Multivariable Prediction Model for the Sexual Function of Cervical Cancer Survivors

Jorge Cea García[1*] iD, M. Carmen Rubio Rodríguez[2] iD, Francisco Márquez Maraver[1] iD, Laura Ríos-Pena[3] iD, Inmaculada Rodríguez Jiménez[1] iD

1. Clinical Management Unit for Obstetrics and Gynecology, University Hospital Virgen Macarena, Seville, Spain
2. Department of Radiation Oncology, HM Hospitals, University Hospital Sanchinarro, Madrid, Spain
3. Institute of Science and Technology, Loyola University, Dos Hermanas, Seville, Spain

## Article Info

## ABSTRACT

**Background & Objective:** Sexual dysfunction is the symptom with the greatest negative impact on the quality of life of cervical cancer survivors. However, the evaluation of sexual function is challenging, and there is ongoing debate concerning its determinants. We aimed to identify predictive variables for sexual function after cervical cancer treatment.

**Materials & Methods:** One hundred and four cervical cancer survivors participated in a prospective cohort study that we carried out employing FACT–Cx v.4.0 and FSFI questionnaires.

**Results:** We developed a beta generalized linear model with a predictive accuracy of 78% (C–index=0.78) and based on vaginal shortening (Cx4) (P=0.077), age (P=0.0002), and ovarian preservation (P=0.01) as risk factors, and functional well–being (P<0.0001) and follow–up duration (P=0.015) as protective factors.

**Conclusion:** To the best of our knowledge, we may have created the first reliable and internally validated prediction model for cervical cancer survivors based on predictors like vaginal shortening, age, ovarian preservation, functional well–being, and follow–up duration that significantly affect female sexual function as targets for potential intervention.

**Keywords:** Nomogram, Sexuality, Surveys and Questionnaires, Uterine Cervical Neoplasms

## Introduction

According to the definition of sexual dysfunction provided by the American Psychological Association, it is "the persistent and recurrent sexual desire and psychophysiological disorders that characterize the sexual response cycle, causing discomfort and difficulties in interpersonal relationships" (1). After finishing their cancer treatments, between 40 and 100 % of cervical cancer survivors experience sexual dysfunction (2, 3).

The evaluation of sexual function becomes extremely important given that cervical cancer patients are relatively young (4–7) and sexually active at the time of diagnosis. In fact, sexual dysfunction has the largest detrimental effect on the quality of life of cervical cancer survivors (8).

Sexual dysfunction is a multifaceted problem that affects many cervical cancer survivors (9, 10) and is influenced by biological, neurological, psychological, social, religious, ethical, cultural, and racial factors (11-19).

Symptoms such as vaginal discharge and bleeding, fear of cancer recurrence, anxiety, and depression may affect sexual function and activity (20–23). On the one hand, premenopausal survivors have more sexual disorders than postmenopausal survivors, which may explain why sexual function is worse in younger survivors than older survivors (24–26). On the other hand, menopausal symptoms and sexual function have not been linked (27, 28). Zhou et al. found that cervical cancer survivors with higher–skilled occupations have better sexual function, which is likely related to a higher educational level and a lesser need for radiation therapy (3).

Sexual function has been associated with the adverse effects of cervical cancer treatment (29, 30), such as fatigue, altered genital and self–body image, pain, lower limb lymphedema (31), and urinary incontinence (32–35). These adverse effects increase the risk of losing independence, altering social relationships, and developing sexual dysfunction (9, 36). However, there is a disagreement regarding the effect of cervical cancer and its treatment on sexual desire (5, 37).

Since the presence of the uterus, ovaries, vagina, and vulva is closely related to self–identity, femininity, and sexuality (38), organic and neurological factors continue to be relevant in the impairment of sexual function in patients undergoing radical hysterectomy (17, 39). Patients undergoing radical hysterectomy are at risk for sexual dysfunction due to comorbidities, particularly intestinal and cardiac conditions (40), advanced age (26), and low educational level, more advanced disease stage (41), absence of ovarian preservation, vaginal shortening, and adjuvant radiation therapy (42). In fact, compared to a radical hysterectomy alone, adjuvant radiation therapy causes more severe and long–lasting sexual dysfunction (43).

Sexual function can be severely harmed by even mild–moderate toxicity (44, 45). Vaginal toxicity, dose-volume histogram characteristics, and sexual function have not been observed to be related (46). Regarding the use of intensity–modulated or three-dimensional conformal radiation therapy, no appreciable alterations in sexual function have been found (47). In patients receiving radiation therapy or concurrent chemoradiotherapy, advanced age increases the risk of sexual dysfunction and decreases sexual activity (8). Married women have much more sexual activity both before and after radiation therapy, according to Yavas et al. (48).

We sought to find the independent sociodemographic, disease–related, and treatment-related determinants of sexual function following cervical cancer treatment because there has not been a published nomogram for predicting sexual function in individuals with this disease.

## Methods

### Study design and population

Between January 1, 2010, and January 31, 2019, we conducted a prospective cohort study on patients with cervical cancer at various clinical stages who underwent various cervical cancer treatment regimens and were monitored at the Outpatient Gynecologic Oncology and Radiation Oncology Clinics of a tertiary hospital. Questionnaires were given out beginning on August 1, 2016. We enrolled 229 subjects after applying the exclusion criteria to 263 potentially eligible patients with cervical cancer, who were chosen to use a successive sampling technique.

Ultimately, 104 respondents were recruited for the prospective female sexual function study.

### Participant selection and assignment

### Inclusion criteria

- Women 18 years or older at the time of the cervical cancer diagnosis

- Histological confirmation of invasive cervical cancer

- Absence of current therapy for cervical cancer

- Ability to read and understand written and/or spoken Spanish

- Normal cognitive function

### Exclusion criteria

- Personal history of or concomitant preoplastic lesion or cancer other than cervical cancer

- Radiotherapy and/or chemotherapy prior to the cervical cancer diagnosis

- Failure to complete questionnaires

- Inability to conduct a regular follow–up of the cervical cancer

### Data collection: study variables, measures, and instruments

We extracted data on sociodemographic and clinical variables and collected clinicopathologic data (stage, treatment modalities, therapy compliance, adverse effects, and routine follow–up visits) from electronic medical records.

Before they signed the informed consent form to participate in the study and agree to publication, the participants were provided pertinent, clear, and concise information about it. The Female Sexual Function Index (FSFI) (49, 50), a sociodemographic questionnaire (51), and the Functional Assessment Cancer Therapy–Cervix (FACT–Cx) (52) version 4.0 questionnaire were given to each participant.

### FACT–Cx

The FACT–Cx v4.0 scale is a combined multidimensional questionnaire (generic and disease-specific), composed of 42 questions, that includes the FACT–General questionnaire (FACT–G), comprised of 27 questions divided into four domains: "physical well–being", "social/familiar well–being", "emotional well–being", and "functional well–being". The FACT–Cx v4.0 includes a domain of "additional concerns" (15 questions) that assesses self–image (B4 and C7) among others. Higher ratings suggest poorer conditions for "additional concerns".

### FSFI

The FSFI multidimensional questionnaire (49, 50) is a specific tool to measure female sexual function, composed of 19 items organized into six domains: two items on sexual desire (questions 1 and 2), four items on sexual arousal (questions 3–6), four items on lubrication (questions 7–10), three items on orgasm (questions 11–13), three items on sexual satisfaction (questions 14–16), and three items on dyspareunia (questions 17 and 18). The score range for items 1, 2, 15, and 16 is 1–5 and 0–5 for the rest, where zero indicates that there was no sexual intercourse during the last 4 weeks. The scores for each domain are added up and multiplied by a predetermined factor to weight each domain equally. The 6 FSFI subscale scores are scaled to have a maximum score of 6. The subscale scores are summed to calculate the FSFI total score, which has a maximum score of 36. Because 4 items have no response option scored 0 (2 items from the desire subscale and 2 from the satisfaction subscale), the minimum possible score for the desire subscale, the satisfaction subscale, and the FSFI total score is greater than 0. Supplementary material I explains missing item data were handled when calculating FSFI scores.

### Interpretation

Higher scores correlate with better female sexual function (53). A total score less than or equal to 26.55 or less than or equal to 3.6 in any domain is diagnostic of female sexual dysfunction (54).

### Properties

According to Rosen et al. (53) and Lou (55), the total score and domains have an excellent initial internal consistency and reliability (Cronbach's α coefficient≥0.82; Cronbach's α coefficient=0.79–0.86, respectively). The outcomes reported by Baser et al. (49) were even better than those shown by Rosen et al. (53), with a Cronbach's α coefficient for the total score and the domains of 0.94 and 0.85–0.94, respectively. This questionnaire has been validated in cervical cancer survivors (10).

We evaluated female sexual function prospectively at several time points throughout the follow–up: baseline scores (recorded when the patient first attended a consultation before the beginning of the cancer treatment) and subsequent evaluations with time intervals of 0–6 (T1), 7–12 (T2), 13–24 (T3), 25–60 (T4), and more than 60 months (T5) after the end of the treatment for cervical cancer. The intervals for the follow-up visits were 0 (T1), 6 (T2), 7–12 (T3), 13–24 (T4), and more than 24 months (T5) since the first consultation for patients who did not fill in the baseline questionnaires. Female sexual function was also studied using the respondents as controls throughout the follow–up period.

### Statistical analyses

The statistical software R (R Foundation for Statistical Computing, Vienna, Austria. R Core Team [2017]) calculated the sample size for detecting statistically significant variations in the within-subject FSFI total scores employing the pwr.t.test function according to conventional effect size from Cohen (56) and clinical studies (d Cohen=0.5; size=medium, effect size=0.5) (57). We should sample at least 64 subjects for a desired power (type 2 error) of 80%, type I error tolerance of 0.05 (level of significance), and hypothesized effect size of 0.5.

We imported the data into the statistical software program R. (R Software Service, INC., USA). Given that the FSFI total score had a non–normal distribution, we developed a beta generalized linear model to evaluate predictors for female sexual function. Based on the scientific evidence and the backward selection of variables significantly associated with the FSFI total score in the univariate linear regression analysis implemented during the feature selection stage [vaginal shortening score on FACT–Cx (Cx4), surgical technique, age, ovarian preservation, fecal incontinence, FACT–Cx functional well–being domain, and follow–up duration], we employed a mixed strategy for selecting predictors, and we validated them by looking at the logistic regression coefficient values and multivariate analyses examining the joint effect of the variables found to correlate with FSFI total score in the univariate analyses.

The loss of follow–up and the impossibility of abstracting information on the sexual function of the women who refused to participate or who could not be recruited was a limiting factor that led to an information bias. But we also conducted an attrition analysis (5, 58) with a weighting strategy for coping with drop–out (59) and a sensitive analysis employing the function of the R package called sensemark (60).

We used a value of the variance inflation factor greater than five as the limit for considering multicollinearity and, consequently, low reliability of the generalized linear model. Discrimination was evaluated using Harrell's concordance index. Lastly, we employed a bootstrap procedure for the internal validation.

We used Spearman's correlation coefficient (ρ) to measure the linear dependence between two quantitative variables with non–parametric distribution or two ordinal variables with 5 levels or more.

All hypothesis tests were 2–tailed. We defined the limit of statistical significance as a P–value less than 0.05.

### Ethical approval

The research project was approved by the Research Ethics Committee of our institution, according to the requirements of Spanish Law 14/2007 of July 3 on biomedical research and the 1964 Declaration of Helsinki.

The research assistant obtained a signed informed consent from each participant for data collection and publication. We will provide our data for independent analysis for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

## Results

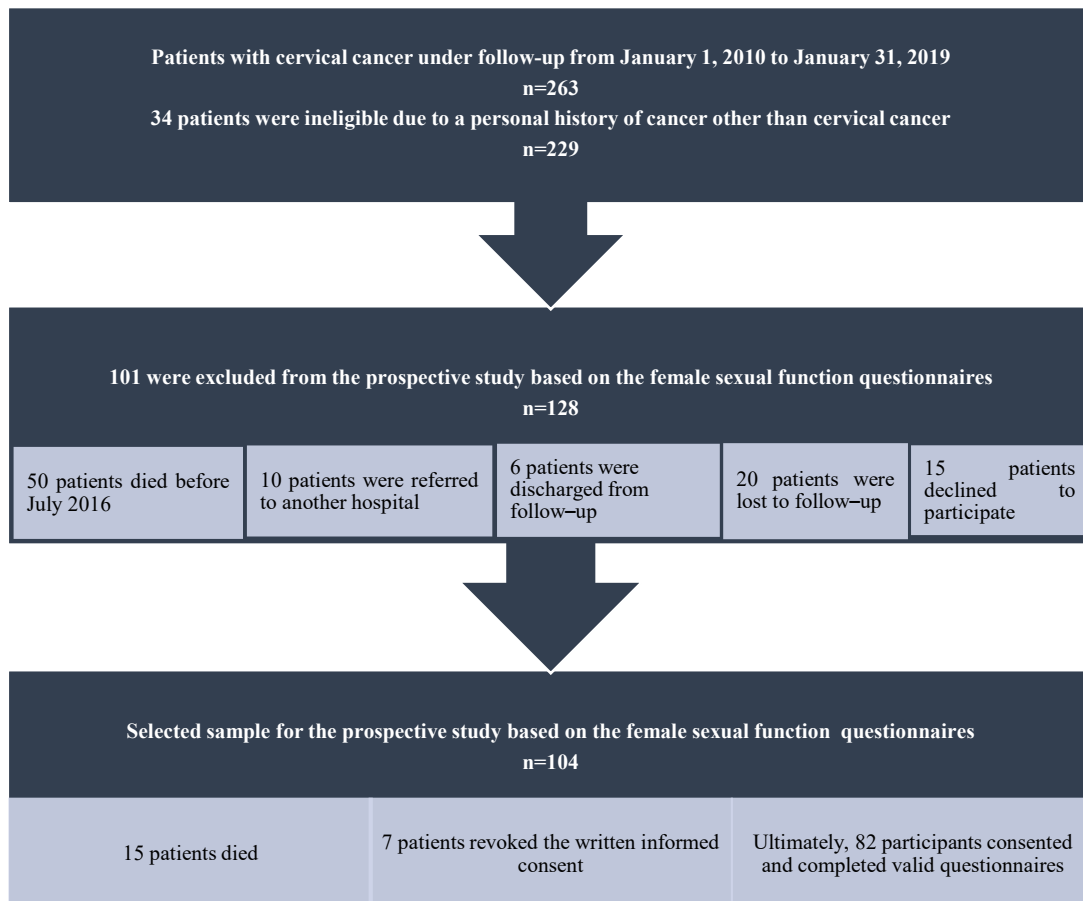Figure 1. shows the flow diagram of the respondents in the prospective study.



**Figure 1. Flow diagram of the study**

### Sociodemographic and disease characteristics

Supplementary material II summarizes the sociodemographic, clinical characteristics, and follow–up duration of the patients with cervical cancer.

Forty–seven and twelve hundredths percent of our study population was sexually active, and the prevalence of female sexual dysfunction was of 60.58%. Table 1. shows the confounding factor's analysis regarding these aforementioned parameters.

### Completion of questionnaires

The questionnaire response rate was 82.81% (median of the time elapsed between the end of the cancer treatment and the application of first questionnaire=24 months, interquartile range=63.5 months). Ten and forty–nine hundredths percent of the patients refused to fill in questionnaires and 6.6% revoked their informed consent to participate throughout the follow–up. Only 4.72% of the respondents consented to complete the baseline questionnaire. There was a severe drop–out in the response rate from T1 to T2, T3, T4 and T5 of 34.91%, 71.7%, 96.23%, and 99.06%, respectively. After the end of the cancer treatment, 8.49%, 5.71 %, 3.33%, and 16.67% of the respondents who filled out questionnaires at T1, T2, T3, and T4 died, respectively. There were 213 questionnaires that were statistically examined in total.

### Impact of cancer treatment-induced morbidity on FSFI scores

The association between cancer treatment-induced fatigue score (FACT–Cx v4.0 GP1) and the FSFI total score was moderately negative ($\rho$=-0.45). FSFI scores were significantly worse in participants with urinary incontinence: arousal (2.4 vs. 5.1 points, P T1=0.036; 2.4 vs. 5.4 points, P T2=0.036), lubrication at T2 (3.06 vs. 5.2 points, P=0.035), orgasm (3.6 vs. 6 points, P T1=0.031; 2.8 vs. 6 points, P T2=0.036), satisfaction (2.72 vs. 5.6 points, P T1=0.01; 2.8 vs. 5.07 points, P T2=0.041), dyspareunia at T2 (2.4 vs.

5.2 points, P=0.036), and total score at T3 (12.57 vs. 24.55 points, P=0.041).

**Table 1.** Confounding factors analysis regarding sexual activity and female sexual dysfunction of cervical cancer survivors

| VARIABLES | Sexually active *vs.* inactive survivors (P) |
|---|---|
| Age | <0.0001 |
| Menopausal status | <0.0001 |
| Marital status | 0.211 |
| Anxiety/depression | 0.181 |
| FACT–Cx v4.0 emotional well–being score | 0.15 |
| Urinary incontinence | 0.459 |
| VARIABLES | Normal sexual function *vs.* sexual dysfunction (P) |
| Educational level | 0.336 |
| Disease stage | 0.524 |
| External beam radiation therapy | 0.337 |
| Brachytherapy | 0.381 |
| Recurrent cervical cancer | 0.064 |

[a]Abbreviations: FACT–Cx, Functional Assessment of Cancer Therapy-Cervix

### Construction, calibration, and validation of a prediction model for female sexual function

We developed a beta generalized linear model to predict the female sexual function based on the FSFI total score that had a continuous probability distribution at T1. We selected this assessment time since it included the most data. The model had a high predictive ability of 78% (Harrell's concordance index=0.78) and was internally validated, without multicollinearity (variance inflation factor=1.05–1.26). Age, ovarian preservation, and vaginal shortening score on the FACT–Cx (Cx4) were included as risk variables. On the other hand, FACT–Cx functional well–being domain score, and follow–up duration were protective variables for female sexual function. Table 2. shows the summary and internal validation of the prediction model.

**Table 2.** Summary and internal validation of the prediction model for overall female sexual function of cervical cancer survivors

| Predictive variables | $\beta_n$ | SEE | z–value | Pr(>\|z\|) | 95% CI | VIF |
|---|---|---|---|---|---|---|
| $\beta_0$ | 15.02 | 7.13 | 2.11 | 0.04 | (1.04, 29.01) | - |
| Vaginal shortening score on FACT–Cx (Cx4) | -1.72 | 0.96 | -1.8 | 0.077 | (-3.6, 0.15) | 1.05 |
| Age | -0.42 | 0.11 | -4 | 0.0002 | (-0.63, -0.22) | 1.26 |
| FACT–Cx v4.0 FWB domain score | 0.84 | 0.19 | 4.49 | <0.0001 | (0.47, 1.2) | 1.05 |
| Follow–up duration | 4.04 | 1.6 | 2.52 | 0.015 | (0.89, 7.18) | 1.19 |
| Ovary preservation | -12.07 | 4.53 | -2.67 | 0.01 | (-20.95, -3.2) | 1.06 |

Residuals:

| Min | 1Q | $M_e$ | 3Q | Max |
|---|---|---|---|---|
| -22.95 | -6.24 | 0.61 | 6.99 | 18.36 |

Residuals of the null model (without predictors): 9785.1 on 60 degrees of freedom

Residuals of the complete model: 4881.6 on 55 degrees of freedom

| Predictive variables | $\beta_n$ | SEE | z–value | Pr(>|z|) | 95% CI | VIF |
|---|---|---|---|---|---|---|
| **AIC: 454.43** | | | | | | |
| **Number of iterations per Fisher score: 2** | | | | | | |
| **202 observations deleted due to missingness** | | | | | | |
| **C–index: 0.78** | | | | | | |
| **Bootstrapping statistics** | | | | | | |
| **R = 5000** | | | | | | |
| **95% CI boot normal (-1.31, 31.32)** | | | | | | |

| Bootstrap estimate | Original (t0) | Bias | SEE |
|---|---|---|---|
| t1 | 15.02 | 0.02 | 8.32 |
| t2 | -1.72 | -0.09 | 0.89 |
| t3 | -0.42 | -0.004 | 0.12 |
| t4 | 0.84 | 0.02 | 0.18 |
| t5 | 4.04 | -0.06 | 1.57 |
| t6 | -12.07 | -0.002 | 5.95 |

[a]**Abbreviations: AIC, Akaike information criterion; $\beta_0$, intercept; $\beta_n$, regression coefficient; C–index, Harrell's concordance index; CI, confidence interval; FACT–Cx, Functional Assessment of Cancer Therapy–Cervix; FWB, Functional well–being; Pr(>|z|): *p*–value; Q, quartile; R, number of repetitions; SEE, standard error estimate; VIF, variance inflation factor; Z, Wald test**

[b]**Bias is a difference between the mean of bootstrap realizations (those from tn), called a bootstrap estimate of T and the value of the statistic in the original dataset (the one from t0).**

[c]**The model's formula has a linear format, as shown in the equation $g(\mu) = \alpha + \beta_1\chi_1 + \ldots \beta_n X_n$, in which the link function $g(\mu)$ (Y) indicates a function of the mean $\mu$ of the probability of distribution of the dependent variable Y. $\mu$ is the expected value or the mean of the dependent variable. The regression coefficients are $\alpha$ and $\beta_1\ldots_n$, in which n is the number of independent predictors. This last expression, if the coefficients are known, allows us to directly calculate $\mu$ for the different values of the independent variable X.**

## Discussion

As far as we are aware, there is no published prediction model for the female sexual function of cervical cancer survivors.

### Predictors of sexual dysfunction in cervical cancer survivors

#### Generic predictors

Sexual activity and function may be impaired by symptoms, such as anxiety and depression **(20–23)**. There were no differences in the rates of sexual activity between survivors who experienced anxiety or depression and those who did not. According to the findings of earlier studies, older age and menopausal status are risk factors for sexual inactivity and dysfunction in our study **(26, 39, 41)**. According to Zhou et al. **(3)**, a higher educational level has a favorable impact on female sexual function. We found no influence, though. Married women engage in much more sexual activity both before and after radiation therapy, according to Yavas et al. **(48)**. We did not discover any differences in sexual activity among marital statuses, though. Unlike the findings published by Hung et al. **(41)**, a more advanced disease stage was not a risk factor for sexual dysfunction in our cohort. According to Huffman et al. **(30)**, recurrent disease impairs sexual function. However, there were no differences between those who experienced recurrences and those who did not in our study.

### Predictors related to adverse effects of cancer treatment

Sexual function of cervical cancer survivors has been associated with adverse effects of cancer treatment **(29, 30)**, including fatigue, changes in genital and self–body image, iatrogenic menopause **(39)**, vaginal shortening **(42)**, and urinary incontinence **(32–35)**, predisposing to a loss of independence, changes in social relationships, and sexual dysfunction **(9, 36)**. In line with the findings of Ratner et al. **(16)**, we found that fatigue and poor functional well–being have a deleterious effect on female sexual function. Juraskova et al. **(39)** found that bilateral oophorectomy worsens sexual function. Our data, however, do not support these findings, most likely because our premenopausal participants are more sexually active and at a higher risk of female sexual dysfunction, which is in line with the findings of Bjelic-Radisic **(6)**. According to our findings, vaginal shortening impairs sexual function, which is consistent with the study by Wang et al. **(42)**. Schover et al. did not discover an association, though **(56)**. In line with the findings of Coyne et al. **(33)**, female sexual function was significantly worse in our participants who had urinary incontinence, even though sexual activity was unaffected by this negative effect.

In comparison to a radical hysterectomy alone, adjuvant radiation therapy causes more severe and long–lasting sexual dysfunction **(43)**. However, there were no differences between survivors with or without sexual dysfunction in the prior use of adjuvant external beam radiation therapy or brachytherapy. Hellsten et al. **(57)** reported that sexual satisfaction does not change within the first year after radiation therapy or surgery, and even sexual dysfunction lasts for a long time after radiation therapy **(58)**. However, other authors have demonstrated that sexual function improves 1 to 2 years after the end of cancer treatment, attaining even higher scores than baseline evaluation. These authors include Bergmark et al. **(59)**, who focused on surgery, and Ferrandina et al. **(60)**, who focused on radiation therapy. The length of the follow–up period had a beneficial effect on our participants' sexual function.

### Strengths and weaknesses

Consecutive sampling method, multiple comparisons, heterogeneous study population in terms of age, follow–up duration, FIGO stage, or treatment modality, memory bias, low baseline response rate, loss to follow–up bias, information bias, and clinical relevance not always being equal to statistical significance are some of the limitations of the current study.

Despite these limitations, this study has several strengths. Due to the study's single–institution design, the data follow a more uniform distribution. Age, menopausal state, comorbidities, follow–up time, disease stage, and non–random dropout analysis were all included in the analyses along with standardized, valid, and reliable outcome indicators. This study's prospective design, following cervical cancer survivors over an extended portion of their life, provides a more comprehensive picture of the disease's consequences for female sexual function.

### Implications for future research and practice

Healthcare providers should take corresponding actions to meet the needs of their patients and improve their quality of life, such as actively treating complications related to cancer therapies and actively selecting vulnerable subpopulations at risk of poor female sexual function and implementing more comprehensive patient care plans for cervical cancer survivors. Our prediction model, once externally validated, could be useful to select these vulnerable subpopulations.

## Conclusion

To conclude, we developed a reliable and internally validated prediction model in cervical cancer survivors based on predictors, such as vaginal shortening, age, ovarian preservation, functional well-being, and follow–up duration that contribute significantly to female sexual function as targets for potential intervention.

Ovarian preservation is supported by level 2++ evidence, according to the American College of Obstetricians and Gynecologists (ACOG), which has given it a recommendation grade of B. According to the European Society of Gynecological Oncology (ESGO), premenopausal women with squamous cell carcinoma and usual adenocarcinoma should be offered this option. Future research should focus on determining the true impact of ovarian preservation on the female sexual function, given that it has little impact on oncological outcomes **(61)** and that there is evidence that it worsens psychological health **(62)**.

## Acknowledgments

## Conflict of Interest

The authors have no competing interests to report.

## Funding

## References

1. Hayes R, Dennerstein L. The Impact of Aging on Sexual Function and Sexual Dysfunction in Women: A Review of Population-Based Studies. J Sex Med. 2005;2(3):317-30. [PMID] [DOI:10.1111/j.1743-6109.2005.20356.x]

2. Park SY, Bae D-S, Nam JH, Park CT, Cho C-H, Lee JM, et al. Quality of life and sexual problems in disease-free survivors of cervical cancer compared with the general population. Cancer. 2007;110(12):2716-25. [DOI:10.1002/cncr.23094] [PMID]

3. Zhou W, Yang X, Dai Y, Wu Q, He G, Yin G. Survey of cervical cancer survivors regarding quality of life and sexual function. J Cancer Res Ther. 2016;12(2):938-44. [PMID] [DOI:10.4103/0973-1482.175427]

4. Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G, et al. Changes in the Demographics and Perioperative Care of Stage IA2/IB1 Cervical Cancer over the Past 16 Years. Gynecol Oncol. 2001;81(2):133-7. [DOI:10.1006/gyno.2001.6158] [PMID]

5. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Early-stage cervical carcinoma, radical hysterectomy, and sexual function. Cancer. 2004;100(1):97-106. [DOI:10.1002/cncr.11877] [PMID]

6. Bjelic-Radisic V, Jensen PT, Vlasic KK, Waldenstrom A-C, Singer S, Chie W, et al. Quality of life characteristics inpatients with cervical cancer. Eur J Cancer. 2012;48(16):3009-18. [DOI:10.1016/j.ejca.2012.05.011] [PMID]

7. Fadhilla HN, Mudigdo A, Rahardjo SS. Effect of age and socio economic status on the quality of life of patients with cervical cancer undertaking chemotherapy at Dr. Moewardi Hospital Surakarta. J Epidemiol Pub Health. 2017;2(1):11-9. [DOI:10.26911/jepublichealth.2017.02.01.02]

8. Korfage IJ, Essink-Bot ML, Mols F, van de Poll-Franse L, Kruitwagen R, van Ballegooijen M. Health-related quality of life in cervical cancer survivors: a population-based survey. Int J Radiat Oncol Biol Phys. 2009;73(5):1501-9. [DOI:10.1016/j.ijrobp.2008.06.1905] [PMID]

9. Carter J, Sonoda Y, Baser RE, Raviv L, Chi DS, Barakat RR, et al. A 2-year prospective study assessing the emotional, sexual, and quality of life concerns of women undergoing radical trachelectomy versus radical hysterectomy for treatment of early-stage cervical cancer. Gynecol Oncol. 2010;119(2):358-65. [PMID] [PMCID] [DOI:10.1016/j.ygyno.2010.07.016]

10. Liu H, Yu J, Chen Y, He P, Zhou L, Tang X, et al. Sexual function in cervical cancer patients: Psychometric properties and performance of a Chinese version of the Female Sexual Function Index. Eur J Oncol Nurs. 2016;20:24-30. [DOI:10.1016/j.ejon.2015.06.007] [PMID]

11. Pauls RN, Kleeman SD, Segal JL, Silva WA, Goldenhar LM, Karram MM. Practice patterns of physician members of the American Urogynecologic Society regarding female sexual dysfunction: results of a national survey. Int Urogynecol J. 2005;16:460-7. [DOI:10.1007/s00192-005-1286-5] [PMID]

12. Safarinejad MR. Female sexual dysfunction in a population-based study in Iran: prevalence and associated risk factors. Int J Impot Res. 2006;18(4):382-95. [DOI:10.1038/sj.ijir.3901440] [PMID]

13. Thiel RdRC, Dambros M, Palma PCR, Thiel M, Riccetto CLZ, Ramos MdF. Tradução para português, adaptação cultural e validação do Female Sexual Function Index. Rev Bras Ginecol Obstet. 2008;30:504-10. [PMID] [DOI:10.1590/S0100-72032008001000005]

14. Laumann EO, Glasser DB, Neves RCS, Moreira ED. A population-based survey of sexual activity, sexual problems and associated help-seeking behavior patterns in mature adults in the United States of America. Int J Impot Res. 2009;21(3):171-8. [DOI:10.1038/ijir.2009.7] [PMID]

15. Serati M, Salvatore S, Uccella S, Laterza RM, Cromi A, Ghezzi F, Bolis P. Sexual Function After Radical Hysterectomy for Early-Stage Cervical Cancer: Is There a Difference between Laparoscopy and Laparotomy?. J Sex Med. 2009;6(9):2516-22. [PMID] [DOI:10.1111/j.1743-6109.2009.01363.x]

16. Ratner ES, Foran KA, Schwartz PE, Minkin MJ. Sexuality and intimacy after gynecological cancer. Maturitas. 2010;66(1):23-6. [DOI:10.1016/j.maturitas.2010.01.015] [PMID]

17. Marcello C, Giovanni R, Emanuela S, Paolo C, Roberto C, Michele P, et al. Pelvic Dysfunctions and Quality of Life after Nerve-sparing Radical Hysterectomy: A Multicenter Comparative Study. Anticancer Res. 2012;32(2):581-8.

18. Afiyanti Y, Milanti A. Physical sexual and intimate relationship concerns among Indonesian cervical cancer survivors: A phenomenological study. Nurs Health Sci. 2013;15(2):151-6. [DOI:10.1111/nhs.12006] [PMID]

19. Briedite I, Ancane G, Ancans A, Erts R. Insufficient Assessment of Sexual Dysfunction: A Problem in Gynecological Practice. Medicina. 2013;49(7):315-20. [DOI:10.3390/medicina49070049]

20. Stead ML, Fallowfield L, Selby P, Brown JM. Psychosexual function and impact of gynaecological cancer. Best Pract Res Clin Obstet Gynaecol. 2007;21(2):309-20. [DOI:10.1016/j.bpobgyn.2006.11.008] [PMID]

21. Distefano M, Riccardi S, Capelli G, Costantini B, Petrillo M, Ricci C, et al. Quality of life and psychological distress in locally advanced cervical cancer patients administered pre-operative chemoradiotherapy. Gynecol Oncol. 2008;111(1):144-50. [DOI:10.1016/j.ygyno.2008.06.034] [PMID]

22. Lau K-L, Yim PH-W, Cheung EY-W. Psychiatric morbidity in Chinese women after cervical cancer treatment in a regional gynaecology clinic. East Asian Arch Psychiatry. 2013;23(4):144-53.

23. Tsatsou I, Parpa E, Tsilika E, Katsaragakis S, Batistaki C, Dimitriadou E, et al. A Systematic Review of Sexuality and Depression of Cervical Cancer Patients. J Sex Marital Ther. 2019;45(8):739-54. [PMID] [DOI:10.1080/0092623X.2019.1610125]

24. Valadares AL, Pinto-Neto AM, Conde DM, Sousa MH, Osis MJ, Costa-Paiva L. A population-based study of dyspareunia in a cohort of middle-aged Brazilian women. Menopause. 2008;15(6):1184-90. [DOI:10.1097/gme.0b013e31817062bc] [PMID]

25. Carter J, Penson R, Barakat R, Wenzel L. Contemporary quality of life issues affecting gynecologic cancer survivors. Hematol Oncol Clin. 2012;26(1):169-94. [PMID] [PMCID] [DOI:10.1016/j.hoc.2011.11.001]

26. Derks M, van Lonkhuijzen LR, Bakker RM, Stiggelbout AM, de Kroon CD, Westerveld H, et al. Long-Term Morbidity and Quality of Life in Cervical Cancer Survivors: A Multicenter Comparison Between Surgery and Radiotherapy as Primary Treatment. Int J Gynecol Cancer. 2017;27(2):350-6. [PMID] [DOI:10.1097/IGC.0000000000000880]

27. Marino JL, Saunders CM, Emery LI, Green H, Doherty DA, Hickey M. Nature and severity of menopausal symptoms and their impact on quality of life and sexual function in cancer survivors compared with women without a cancer history. Menopause. 2014;21(3):267-74. [DOI:10.1097/GME.0b013e3182976f46] [PMID]

28. Lee Y, Lim MC, Kim SI, Joo J, Lee DO, Park SY. Comparison of Quality of Life and Sexuality between Cervical Cancer Survivors and Healthy Women. Cancer Res Treat. 2016; 48(4):1321-9. [DOI:10.4143/crt.2015.425] [PMID] [PMCID]

29. Burns M, Costello J, Ryan-Woolley B, Davidson S. Assessing the impact of late treatment effects in cervical cancer: an exploratory study of women's sexuality. Eur J Cancer Care. 2007; 16(4):364-72. [PMID] [DOI:10.1111/j.1365-2354.2006.00743.x]

30. Huffman LB, Hartenbach EM, Carter J, Rash JK, Kushner DM. Maintaining sexual health throughout gynecologic cancer survivorship: A comprehensive review and clinical guide. Gynecol Oncol. 2016;140(2):359-68. [PMCID] [DOI:10.1016/j.ygyno.2015.11.010] [PMID]

31. Stolldorf DP, Dietrich MS, Ridner SH. Symptom frequency, intensity, and distress in patients with lower limb lymphedema. Lymphat Res Biol. 2016;14(2):78-87. [DOI:10.1089/lrb.2015.0027] [PMID] [PMCID]

32. Yip S-K, Cardozo L. Psychological morbidity and female urinary incontinence. Best Pract Res Clin Obstet Gynaecol. 2007;21(2):321-9. [DOI:10.1016/j.bpobgyn.2006.12.002] [PMID]

33. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int. 2008;101(11):1388-95. [PMID] [DOI:10.1111/j.1464-410X.2008.07601.x]

34. Egil Skjeldestad F, Hagen B. Long-term consequences of gynecological cancer treatment on urinary incontinence: a population-based cross-sectional study. Acta Obstet Gynecol Scand. 2008;87(4):469-75. [DOI:10.1080/00016340801948326] [PMID]

35. Ratner ES, Erekson EA, Minkin MJ, Foran-Tuller KA. Sexual satisfaction in the elderly female population: A special focus on women with gynecologic pathology. Maturitas. 2011; 70(3):210-5. [PMID] [PMCID] [DOI:10.1016/j.maturitas.2011.07.015]

36. Abbott-Anderson K, Kwekkeboom KL. A systematic review of sexual concerns reported by gynecological cancer survivors. Gynecol Oncol. 2012;124(3):477-89. [DOI:10.1016/j.ygyno.2011.11.030] [PMID]

37. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2003;56(4):937-49. [DOI:10.1016/S0360-3016(03)00362-6] [PMID]

38. Juraskova I, Butow P, Robertson R, Sharpe L, McLeod C, Hacker N. Post-treatment sexual adjustment following cervical and endometrial cancer: a qualitative insight. Psychooncology. 2003;12(3):267-79. [DOI:10.1002/pon.639] [PMID]

39. Song T, Choi CH, Lee Y-Y, Kim T-J, Lee J-W, Kim B-G, et al. Sexual Function After Surgery for Early-Stage Cervical Cancer: Is There a Difference in it According to the Extent of Surgical Radicality?. J Sex Med. 2012;9(6):1697-704. [DOI:10.1111/j.1743-6109.2012.02723.x] [PMID]

40. Shin DW, Nam JH, Kwon YC, Park SY, Bae D-S, Park CT, et al. Comorbidity in Disease-Free Survivors of Cervical Cancer Compared with the General Female Population. Oncology. 2008;74(3-4):207-15. [DOI:10.1159/000151368] [PMID]

41. Hung M-C, Wu C-L, Hsu Y-Y, Hwang J-S, Cheng Y-M, Wang J-D. Estimation of potential gain in quality of life from early detection of cervical cancer. Value Health. 2014;17(4):482-6. [DOI:10.1016/j.jval.2014.02.006] [PMID]

42. Wang X, Chen C, Liu P, Li W, Wang L, Liu Y. The morbidity of sexual dysfunction of 125 Chinese women following different types of

radical hysterectomy for gynaecological malignancies. Arch Gynecol Obstet. 2018;297: 459-66. [DOI:10.1007/s00404-017-4625-0] [PMID]

43. Shu-Qin C, Ling-Zhi K, Hong-Ye J, Li F, Jun C, Shu-Zhong Y. Early Cervical Cancer Impact of Peritoneal Vaginoplasty Combined With Laparoscopic Radical Hysterectomy Improved Sexual Function. Int J Gynecol Cancer. 2015; 25(3):526-32. [DOI:10.1097/IGC.0000000000000366][PMID]

44. Vaz AF, Pinto-Neto AM, Conde DM, Costa-Paiva L, Morais SS, Pedro AO, et al. Quality of life and menopausal and sexual symptoms in gynecologic cancer survivors: a cohort study. Menopause. 2011;18(6):662-9. [DOI:10.1097/gme.0b013e3181ffde7f] [PMID]

45. Hofsjö A, Bergmark K, Blomgren B, Jahren H, Bohm-Starke N. Radiotherapy for cervical cancer - impact on the vaginal epithelium and sexual function. Acta Oncol. 2018;57(3):338-45. [DOI:10.1080/0284186X.2017.1400684] [PMID]

46. Singh R, Chopra S, Engineer R, Paul S, Kannan S, Mohanty S, et al. Dose-volume correlation of cumulative vaginal doses and late toxicity after adjuvant external radiation and brachytherapy for cervical cancer. Brachytherapy. 2017;16(4): 855-61. [DOI:10.1016/j.brachy.2017.03.008] [PMID]

47. Mohanty SK, Chopra S, Mudaliar A, Kannan S, Mahantshetty U, Engineer R, et al. A comparative analysis of quality of life after postoperative intensity-modulated radiotherapy or three-dimensional conformal radiotherapy for cervical cancer. Indian J Cancer. 2018;55(4): 327-35. [DOI:10.4103/ijc.IJC_453_17] [PMID]

48. Yavas G, Yavas C, Dogan NU, Ilhan TT, Dogan S, Karabagli P, et al. Pelvic radiotherapy does not deteriorate the quality of life of women with gynecologic cancers in long-term follow-up: A 2 years prospective single-center study. J Cancer Res Ther. 2017;13(3):524-32.

49. Baser RE, Li Y, Carter J. Psychometric validation of the female sexual function index (FSFI) in cancer survivors. Cancer. 2012; 118(18):4606-18. [DOI:10.1002/cncr.26739] [PMID]

50. Stephenson KR, Toorabally N, Lyons L, M. Meston C. Further Validation of the Female Sexual Function Index: Specificity and Associations With Clinical Interview Data. J Sex Marital Ther. 2016;42(5):448-61. [PMID] [DOI:10.1080/0092623X.2015.1061078]

51. Castillo-Ávila IY, Canencia-Padilla J, Zurbarán-Lamadrid M, Pertuz-Cantillo D, Montes-Padilla M, Jiménez-Chacón E. Quality of life in women with cervical cancer, Cartagena (Colombia), 2012. Revista Colomb de Obstet y Ginec. 2015; 66(1):22-31. [DOI:10.18597/rcog.4]

52. Cella D, Hernandez L, Bonomi AE, Corona M, Vaquero M, Shiomoto G, et al. Spanish language translation and initial validation of the functional assessment of cancer therapy quality-of-life instrument. Med Care. 1998;36(9):1407-18. [PMID] [DOI:10.1097/00005650-199809000-00012]

53. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function. J Sex Marital Ther. 2000;26(2):191-208. [DOI:10.1080/009262300278597] [PMID]

54. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): Cross-Validation and Development of Clinical Cutoff Scores. J Sex Marital Ther. 2005;31(1):1-20. [DOI:10.1080/009262305090475206] [PMID]

55. Lou Q. Sexual dysfuncion in women with type 2 diabetes in 3A hospitals in Hangzhou. Hangzhou: Med Sch Zhejiang Univ. 2010.

56. Schover LR, Fife M, Gershenson DM. Sexual dysfunction and treatment for early stage cervical cancer. Cancer. 1989;63(1):204-12. [PMID][DOI:10.1002/1097-0142(19890101)63:13.0.CO;2-U]

57. Hellsten C, Lindqvist PG, Sjöström K. A longitudinal study of sexual functioning in women referred for colposcopy: a 2-year follow up. BJOG: Int J Obstet Gynaecol. 2008; 115(2):205-11. [PMID] [DOI:10.1111/j.1471-0528.2007.01503.x] [DOI:10.1111/j.1471-0528.2007.01609.x]

58. Shuang Y, Jiaxin Y, Dongyan C, Jinghe L, Keng S. A Systematic Review of Quality of Life and Sexual Function of Patients With Cervical Cancer After Treatment. Int J Gynecol Cancer. 2014;24(7):1146. [PMID] [DOI:10.1097/IGC.0000000000000207]

59. Bergmark K, Åvall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. New Eng J Med. 1999;340(18): 1383-9. [DOI:10.1056/NEJM199905063401802][PMID]

60. Ferrandina G, Mantegna G, Petrillo M, Fuoco G, Venditti L, Terzano S, et al. Quality of life and emotional distress in early stage and locally advanced cervical cancer patients: A prospective, longitudinal study. Gynecol Oncol.

2012;124(3):389-94. [DOI:10.1016/j.ygyno.2011.09.041] [PMID]

61. Signorelli M, Bogani G, Chiappa V, Ditto A, Scaffa C, Martinelli F, et al. Ovarian preservation in locally advanced cervical cancer undergoing neoadjuvant chemotherapy and radical surgery. Minerva Ginecol. 2018;70(4):

357-63. [PMID] [DOI:10.23736/S0026-4784.18.04221-1]

62. Li C, Samsioe G, Iosif C. Quality of life in long-term survivors of cervical cancer. Maturitas. 1999;32(2):95-102. [PMID] [DOI:10.1016/S0378-5122(99)00020-1]

**How to Cite This Article:**

Cea García, J., Rubio Rodríguez, M. C., Márquez Maraver, F., Ríos-pena, L., Rodríguez Jiménez, I. Development and internal validation of a multivariable prediction model for the sexual function of cervical cancer survivors. J Obstet Gynecol Cancer Res. 2024;9(2):201-11.

**Download citation:**     **RIS** | **EndNote** | **Mendeley** |**BibTeX** |