

Original Research

Cervical Cancer in Women Aged 35 Years and Younger

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ABSTRACT

Purpose: Age has been evaluated as a prognostic factor in cervical cancer in both hospital- and population-based studies. Results regarding the relation of age and cervical cancer prognosis are conflicting. This study pursued a contemporary assessment of the association of extreme young age at the time of a cervical cancer diagnosis on survival.

Methods: Institutional review board approval was obtained, and retrospective data collection at 2 academic institutions was performed. Inclusion criteria involved women ≤ 35 years diagnosed with cervical cancer between 1990 and 2012. Data included demographic and prognostic information pertinent to survival and progression. Characteristics of very young (≤ 25 years) and young (> 25 –35 years) women were compared. Kaplan-Meier estimates, the log-rank test, and Cox proportional hazards modeling were used to assess the association of age, tumor histology, grade, stage, and parametrial involvement with progression-free survival (PFS) and overall survival (OS).

Findings: Incident cases ($n = 126$) of cervical cancer in patients ≤ 35 years of age were identified of which complete clinical information was available for 114 women. Fifteen percent (17 of 114) were ≤ 25

years, with the remaining 85% (97 of 114) being 26 to 35 years of age. Race, smoking status, and marital status were comparable between the 2 groups. Squamous histology dominated overall (77 of 114; 68%) with adenocarcinoma contributing $\sim 25\%$ (30 of 114; 26%) of cases. The majority (96 of 114, 84%) had either stage 1A (31 of 114, 27%) or 1B (65 of 114, 57%) disease. A log-rank test revealed no evidence to infer a difference in either PFS or OS among the age groups ($P = 0.511$ and $P = 0.340$). In a univariate analysis, grade and stage significantly affected OS ($P < 0.0001$, $P = 0.045$), and stage significantly affected PFS ($P < 0.0001$). In multivariate modeling, presence of parametrial involvement and histologic cancer type significantly affected both PFS ($P = 0.002$, $P = 0.001$) and OS ($P = 0.001$, $P = 0.001$).

Implications: Tumor histology, parametrial involvement, and stage continue to be strong prognosticators for PFS and OS. Progression and survival outcomes are age independent in women with cervical cancer ≤ 35 years of age. Further study of a larger young cohort may potentially yield different outcomes. (*Clin Ther.* 2016;38:459–466) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: age, cervical cancer, progression, survival, young women.

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INTRODUCTION

Cervical cancer, although largely preventable, is the most common site of gynecologic malignancy in women <35 years of age in the United States. Worldwide, cervical cancer is second only to breast cancer in cancers that affect women.¹ Young patient age has been posited as a risk factor for more aggressive cervical cancers. Alternatively, although no genetic predisposition for cervical cancer has been accepted, researchers have proposed that there is a heritable inability to clear human papillomavirus (HPV) infection because population studies have found an increased incidence of cervical cancer in some families. In a Swedish study of >9000 siblings or half-siblings with cervical cancer or dysplasia, 64% of cases were attributed to genetics and only 36% to environmental exposures.² It seems improbable for young women to develop advanced disease, given the classic teaching that the risk of progression from mild dysplastic changes of the cervix to severe dysplasia, let alone cancer, is only 1% per year.³ Therefore, the development of cancer in young women, especially the very young, has led to the theory that cervical cancer in the very young must be more aggressive.⁴ Others blame changes in sexual behavior with an earlier age of first intercourse, greater frequency of multiple partners and HPV infection, and tobacco use for the observations.^{5–8} Current estimates put the prevalence of HPV (all types) at 59% in 20- to 24-year-old women and 50% in 25- to 29-year-old women.⁹

Several investigators have examined the relation between age at diagnosis and prognosis with conflicting results. In a study by Rutledge et al,¹⁰ 250 women ≤35 years were matched by stage and treatment to older women. Younger women with advanced stage disease were noted to have worse overall survival (OS), yet they survived longer when diagnosed with early-stage disease. Conversely, Clark et al¹¹ concluded that cervical cancer behaved more aggressively in their comparison of 41 women ≤35 years old with 96 women aged ≥36 years in that there was a higher incidence of nodal metastases observed in the younger patients despite less-advanced clinical stage of disease. Paradoxically, they simultaneously observed that youth conferred better survival outcomes overall. In other studies, clinical behavior was age independent, but these studies compared women <35 years with older women.^{12–14} Our hypothesis is that cervical cancer in the very young (women <25 years) is a more aggressive disease.

We sought to evaluate the relation of very young age to aggressiveness of cancer by comparing the young with the very young. This is a contemporary investigation after changes to practice that followed the 1999 National Cancer Institute alert that all patients with cervical cancer treated with radiation should also receive sensitizing cisplatin.

The primary objective of this study was to assess the effect of age on progression-free survival (PFS) and OS in women with cervical cancer ≤35 years of age. Secondly, we sought to evaluate the impact of tumor histology, grade, stage, and parametrial involvement on PFS and OS in this cohort.

METHODS

Retrospective data collection was performed after approval from the institutional review boards at 2 tertiary academic medical centers (University of Virginia Health System, Charlottesville, VA; University of North Carolina, Chapel Hill, NC). Data for patients with cervical cancer aged ≤35 years treated between 1990 and 2012 were abstracted.

Chart review included abstraction of demographic information (age, race, smoking status, and marital status), disease characteristics (histology, grade, stage, parametrial involvement), treatment history (surgery, radiation, chemotherapy, combination), and outcome data (OS and time to recurrence).

To assess the primary outcome of the effect of age on PFS and OS, patients were classified according to age at diagnosis. These age groups were defined as very young (≤25 years old) and young (>25–35 years old) women. PFS was defined as the time from date of diagnosis to disease progression or death from any cause. OS was defined as the time from date of diagnosis to death from any cause. Secondary outcomes included assessing the effect of tumor histology, grade, stage, and parametrial involvement on PFS and OS.

Differences in OS and PFS among the age groups were evaluated with Kaplan-Meier survival estimates and the log-rank test. Multivariate Cox proportional hazards modeling was used to perform time-to-event analysis of OS and PFS, including the predictors tumor histology, parametrial involvement, and age. Tumor grade was not stated for >20% of women, and some subgroups of stage were too small and observed no events, so these variables were excluded from our final multivariate model. Significance was

determined with a Wald test, and differences were considered significant for P values (2-sided) ≤ 0.05 . Assumptions of the Cox proportional hazards model were assessed with graphical methods.

RESULTS

A total of 126 women with cervical cancer were identified from the 2 institutions. Complete clinical information was available for 114 women, and they comprise the study group. Approximately 15% (17 of 114) were very young, with the remaining 85% (97 of 114) belonging to the young group. Despite a 23-year searchable study time frame, the oldest case in the final cohort dated back to 1998. Demographic and clinical characteristics are summarized in [Table I](#).

The mean age at diagnosis was 29.7 years (median, 30 years; range, 17–35 years). The majority of patients were Caucasian (~75%), 13% were black, and 11% were Hispanic. Nearly half were married. Most patients were never-smokers. Of the 114 with data available, 22% of women were nulliparous, and parity was ≥ 2 in 63% of the cohort.

Squamous histology dominated overall (68%) with adenocarcinoma contributing ~25% of cases. Squamous histology was present in 10 of the 17 very young women (58%) versus 67 of the 97 young women (69%) with adenocarcinoma being the next most prevalent (4 of 17, 24% and 26 of 97, 27%, respectively). There were 5 cases of small cell carcinoma with 2 occurring in women <25 years of age.

More than 80% of women in both groups had early-stage disease (stage 1A or 1B). Of the 109 women for whom a description of parametrial disease extension was available, only 15 had involvement, and this was unrelated to patient age. Of the 88 patients for whom tumor grade was stated, cancers were more often grade 2 (35 of 88, 40%) or grade 3 (35 of 88, 40%), with only 20% (18 of 88) being grade 1.

Associations of age with PFS and OS, as assessed by Kaplan-Meier estimation, are presented in [Figures 1A](#) and [1B](#). Neither PFS (log-rank $P = 0.511$) nor OS (log-rank $P = 0.340$) were significantly different by age group (≤ 25 vs > 25 years old).

The entire cohort had a 5-year OS rate of 42.1% (48 of 114). When analyzed according to disease distribution, this equated to a rate of 46% for patients

Table I. Patient demographic and clinical characteristics (N = 114).

Characteristic	Value
Mean age at diagnosis (range), years	29.7 (17–35)
Race, n (%)	
Caucasian	86 (75.4)
Black	15 (13.2)
Hispanic	13 (11.4)
Marital status, n (%)	
Single	39 (34.2)
Married	55 (48.2)
Divorced	13 (11.4)
Widowed	1 (0.88)
Unknown	6 (5.3)
Smoking status, n (%)	
Current	35 (30.7)
Former	13 (11.4)
Never	62 (54.4)
Unknown	4 (3.5)
Stage at diagnosis, n (%)	
1A1	25 (21.9)
1A2	6 (5.3)
1B1	37 (32.5)
1B2	28 (24.5)
IIA1	0
IIA2	2 (1.7)
IIB	10 (8.7)
IIIA	0
IIIB	4 (3.5)
IV	2 (1.7)
Histology, n (%)	
Squamous	77 (67.5)
Adenocarcinoma	30 (26.3)
Small cell	5 (4.4%)
Adenosquamous	2 (1.7)
Grade, n (%)	
1	18 (15.8)
2	35 (30.7)
3	35 (30.7)
Unknown	26 (22.8)
Parametrial involvement, n (%)	
No	94 (82.5)
Yes	15 (13.2)
Unknown	5 (4.4)

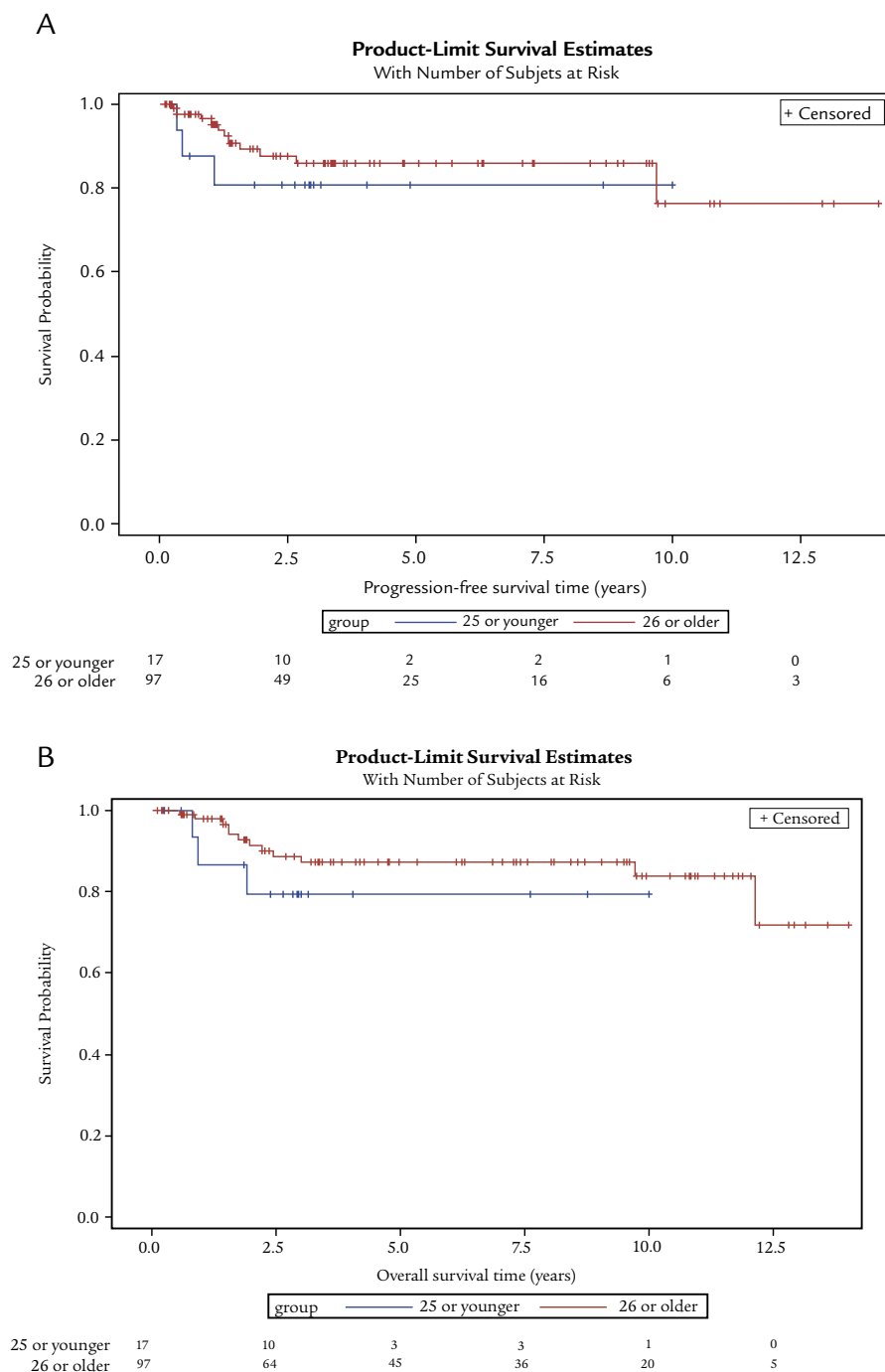


Figure 1. (A) Kaplan-Meier survival graphs of age versus progression-free survival ($P = 0.511$). (B) Kaplan-Meier survival graphs of age versus overall survival ($P = 0.340$).

with localized disease, 25% for patients with regionalized disease, and 0% for patients with distant disease. In univariate analyses (Table II), PFS and

OS were evaluated across 5 categories of stage (1A1, 1A2, 1B1, 1B2, and stage II to IV) and 3 levels of tumor grade (1–3). Higher tumor grade conferred an

Table II. Univariate analysis of key variables and clinical outcomes.

Variable	Progression-free survival	Overall survival
Stage	<0.0001	<0.0001
Grade	0.053	0.0455

Reported as *P* values.

increased risk of recurrence or progression. As stage increased, recurrence increased, and survival decreased. Both stage and grade significantly affected OS ($P < 0.0001$, $P = 0.045$), and stage significantly affected PFS ($P < 0.0001$). A trend was found toward grade significantly affecting PFS; however, this relation did not reach statistical significance ($P = 0.053$).

Cox proportional hazard modeling (Table III) of variables associated with PFS or OS indicated that there was no association between age and PFS (hazard ratio [HR] = 1.07; $P = 0.315$) or OS (HR = 1.05; $P = 0.468$). Absence of parametrial involvement was associated both with improved PFS (HR = 8.71; $P = 0.002$) and OS (HR = 7.39; $P = 0.001$). Approximately 40% of patients with parametrial involvement recurred or progressed compared with only 10% of patients without parametrial involvement. Results from the multivariate model in Table III indicate that both squamous and adenocarcinoma tumor histology were associated with

improved PFS and OS. Women with adenocarcinoma were the least likely to recur or progress (3%) compared with 14% of women with squamous histology and 57% of women with other histologic types.

CONCLUSIONS

According to estimates, cervical cancer is the most common gynecologic malignancy in women <35 years old with an incidence of 16.5 per 100,000.^{15,16} An abnormal Pap smear or cervical biopsy was the presenting complaint in nearly 60% of women in our cohort. This finding provides additional support for the need for continued screening in this young population to the extent set forth by the American College of Obstetricians and Gynecologists.¹⁷ In addition to screening, efforts at primary prevention via HPV vaccination should continue. Large clinical trials have found HPV vaccination to be effective in preventing cervical disease associated with HPV-16 and HPV-18; however, immunization is most beneficial in HPV-naïve women.¹⁸ Screening remains important because ~25% of cancers will not be prevented by earlier vaccine types that did not immunize against all HPV types.

For women found to have cervical cancer, our findings indicate age at diagnosis in and of itself in women ≤35 years of age is not associated with a worse prognosis (Table III). Because there were only 17 patients <25 years of age in the very young cohort, statistical difference may not have been noted, but that group did have worse survival rates, as displayed in Figures 1A and 1B. In addition both

Table III. Multivariate analysis of key variables and clinical outcomes.

Variable	PFS		OS	
	Hazard ratio	<i>P</i>	Hazard ratio	<i>P</i>
Histology*		0.001 [†]		0.001 [†]
Squamous	0.066	0.001	0.069	0.0009
Adenocarcinoma	0.035	0.004	0.022	0.002
Parametrial involvement	8.710	0.002	7.395	0.001
Age	1.071	0.315	1.05	0.468

*The reference group is 'Other' tumor histology.

[†]Cumulative *P* value for all histology types.

groups fared worse than survival in older women. The percentage of women surviving ≥ 5 years in this study according to local and regional disease was 46% and 25%, respectively, compared with historic 5-year relative survival by stage at diagnosis for women ≥ 50 years of age of 87% for localized disease and 54% for regional disease.¹⁹ This could point to a different disease pathway in younger women, leading to a more aggressive disease due to host or other unknown factors.

Similar to their older counterparts, tumor grade and histology affected prognosis and specifically PFS in our cohort. Analogous to patients with cervical cancer of all ages, squamous histology predominated in nearly 68% of cases in this study, and 26% of patients had adenocarcinoma.²⁰ Compared with historic trends, this rising proportion of invasive adenocarcinoma especially in younger white women is consistent with the findings of other researchers.^{21,22} This may be due to greater recognition and more awareness of adenocarcinoma and improved detection of its precursor lesions through better endocervical sampling techniques.²³

It has been reported that adenocarcinoma confers poorer survival rates than squamous cell carcinoma, particularly for patients with regional disease.^{21,24} All patients in our study with adenocarcinoma had localized disease, and cases were fairly evenly distributed among the 2 age groups. Despite the absence of adenocarcinoma histology in women having regional and distant disease, we found that histology still substantially affected OS and that the aggregate histologic proportions were similar to larger population-based studies.

More than 2% of patients in this study had small cell carcinoma. Historically, this rare and aggressive histology has been observed to occur at a mean incidence of only 0.06 per 100,000 women; thus, its substantially higher rate in this series may affect our findings.²⁵ Nevertheless, although the recent work of Castanon et al²⁶ in a series that examined 1800 cases of cervical cancer in women aged 20 to 29 years between 2007 and 2012 found a low non-squamous, non-adenocarcinoma, and non-adenosquamous rate of 2%, the rare histologic subtypes were most commonly found in the youngest women in the series, aged 20 to 24 years, at a rate of nearly 6%. Furthermore, 20% of the time, these younger women were diagnosed at a higher stage of disease (stage ≥ 2)

compared with frequencies of $\sim 4\%$ and 7% for their older counterparts (age 25 years and age 26–29 years, respectively). This trend was similar in our study with 17% of patients aged 20 to 29 years having been diagnosed at stage ≥ 2 .

Nearly 30% of cases in the youngest women occurred in those ≤ 20 years old. This is in contrast to an analysis of national surveillance data by Bernard et al²⁷ in which 1% of cervical carcinoma was diagnosed in this young age range. This discrepancy may indicate a regional variation in our patient cohort or may be due to referral bias of younger, higher risk women to academic medical centers and thus may limit the generalizability of our findings.

Recent evidence from Japan epidemiologic data found a higher risk of death from cervical cancer in a younger cohort. This population-based cancer registry study covered 9 million people in a single geographic area in Japan.²⁸ If the aggressiveness and presence of cervical cancer in a young woman is due to a genetic alteration, we would expect that would most likely be seen in regional studies such as the Japanese study compared with the genetically diverse population in the United States. There does appear to be an association of cervical cancer with a large variety of polymorphisms in a wide variety of genes, including genes that regulate immunity and susceptibility,²⁹ cytokine production,^{30,31} angiogenesis, tumor suppressor pathways,^{32,33} and signal transducer and activator of transcription pathways.³⁴ Investigations are ongoing to identify genetic alterations that may make women less likely to clear persistent HPV infections and more susceptible to the development of cervical cancer.

This study did not include a comparison group because it was our primary intention to determine whether degree of youth was clinically affected. Lymphovascular space invasion (LVSI) status was unknown for $\sim 50\%$ of the young women and for $>25\%$ of the very young women. Of the results available, 3 of 15 (20%) of very young women and 22 of 97 (23%) of the young women had positive LVSI. Complete data about LVSI may have led to a different interpretation of our results. Information about insurance coverage, income, and social issues related to care compliance was not collected, and this may influence the results seen in these young women. Omission of details of treatment such as time to completion of therapy for those treated with

chemoradiation and analysis not according to treatment modality are other weaknesses. All 3 cases eligible for treatment with chemosensitization diagnosed before the 1999 National Cancer Institute alert had received cisplatin. In addition, we recognize that this study is limited by the small numbers of cases, and additional multi-institutional studies may clarify these findings. Nonetheless, our findings offer further hypothesis-generating data and serve to emphasize the importance of considering disease distribution, tumor histology, and grade when determining prognosis in young patients.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article. No financial support or funding was provided for this project.

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