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Young age as a prognostic factor in cervical cancer: Results of a population-based study

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OBJECTIVE: Our goal was to use population-based data to determine the difference in 5-year survival in women diagnosed with cervical cancer between those aged 18-34 years and those aged 40-60 years.
STUDY DESIGN: The SEER (Surveillance, Epidemiology, and End Results) public-use database, 1973-1994, was used for this investigation. Only subjects with cervical carcinoma diagnosed between 1988 and 1990 were included. Subjects were stratified on age at diagnosis (<35 years or 40-60 years), clinical stage, histologic type, race-ethnicity, and grade.
RESULTS: Two thousand cases of invasive cervical cancer were identified. The younger subgroup of patients was diagnosed with earlier-stage disease more frequently than the older group ($P = .0001$). When adjustments were made for non–cervical cancer causes of death, there was no difference in 5-year survival between the 2 cohorts. African American women had a poorer 5-year survival ($P = .02$)
CONCLUSION: There was no overall difference in survival between the 2 cohorts when appropriate adjustments were made for cause of death and for stage, histologic type, and grade of disease. (Am J Obstet Gynecol 1999;180:1464-7.)

Key words: Cervical cancer, young age as a prognostic factor, outcome

Cervical cancer is the third most common genital tract malignancy in US women. The incidence increases from 2.2 to 13.3 per 100,000 below age 35 years to 21.2 per 100,000 between the ages of 40 and 60 years. Young women with the diagnosis of cervical cancer have been perceived as having a poorer outcome. This general observation is in agreement with the observation that the diagnosis of many female genital tract malignancies in youth portends a worse prognosis in comparison with diagnosis of similar diseases at a later age.

Previous reports have suggested that the worse prognosis among young women with cervical cancer can be attributed to the greater frequency of poorly differentiated cancers identified in this subgroup and the more advanced disease at presentation.[1, 2] Studies to date have utilized subjects accumulated over several decades in the remote past.[3, 4] These reports are compromised by the small number of cases, the specificity of the disease stage analyzed, and changes in treatment, and they are representative of hospital-based analyses.[3-6]

Determination of the effect of age on outcome is complicated by several related issues including the risk of death from competing age-related illnesses, stage of disease, method of treatment, and histologic type. The objective of this study was to perform a population-based comparison of the survival outcome in women with cervical cancer with the use of the nationally recognized SEER (Statistical, Epidemiologic, and End Results) database. The SEER program of the National Cancer Institute prospectively collects and publishes cancer incidence data from population-based cancer registries covering approximately 14% of the US population. The areas reported are selected for their epidemiologically significant population subgroups and their ability to maintain a population-based cancer reporting system.

Material and methods

Study subjects. The SEER Cancer Incidence Public-Use Database 1973-1994 was used for this analysis. Subjects with invasive cervical carcinoma diagnosed between 1988 and 1990 who were ≤60 years old were identified. Before 1988 SEER did not uniformly publish information from the American Joint Commission on Cancer (AJCC) staging system; therefore subjects diagnosed with cervical cancer before this year were excluded. Subjects were excluded if there was no information regarding the

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Table I. Characteristics of patients with cervical cancer

Variable	*Group 1: Age <35 y*	*Group 2: Age 40-60 y*
No. of subjects	696	1304
Mean age (y)	33	48
Race*		
African American	82 (12%)	184 (15%)
Asian American	17 (3%)	75 (6%)
Caucasian	529 (78%)	889 (72%)
Hispanic	48 (7%)	88 (7%)
Histologic type ($P = .01$)		
Squamous cell carcinoma	581 (83%)	1027 (79%)
Adenocarcinoma	115 (17%)	277 (21%)
Stage at diagnosis ($P = .001$)		
I	561 (81%)	771 (59%)
II	39 (6%)	233 (18%)
III	75 (11%)	186 (14%)
IV	21 (3%)	114 (9%)
Tumor grade		
1	39 (6%)	89 (7%)
2	121 (17%)	292 (22%)
3	131 (19%)	302 (23%)
4	12 (2%)	23 (2%)
Unknown	393 (56%)	598 (46%)

*Eighty-eight patients could not be characterized by ethnicity. Twenty of these patients were in group 1 and 68 in group 2.

Table II. Cox proportional hazards model

Variable	*Risk ratio*	*95% confidence interval*	*Statistical significance*
Age		0.74-1.22	$P = .67$
40-60 y	1.00		
<35 y	0.94		
Race			
Caucasian	1.00	—	—
African American	1.37	1.04-1.80	$P = .02$
Asian American	0.73	0.41-1.28	$P = .27$
Hispanic	0.86	0.56-1.34	$P = .37$
Histologic type		0.79-1.38	$P = .78$
Squamous cell carcinoma	1.00		
Adenocarcinoma	1.05		
Tumor grade			
1	1.00	—	—
2	1.74	0.90-3.37	$P = .10$
3	1.89	0.98-3.65	$P = .06$
4	3.54	1.60-7.84	$P = .001$

AJCC staging or if the follow-up period was unknown. Patients with cancer diagnosed after 1990 were excluded to provide every subject the opportunity to attain at least 4 years of follow-up. These women were further stratified into 2 age groups. Group 1 comprised women diagnosed with cervical cancer between the ages of 16 and 34 years. Women in whom the diagnosis of invasive cervical cancer was made between the ages of 40 and 60 years composed group 2. Subjects who did not fall into these 2 groups were excluded from analysis because the intent of the study was to compare the 2 different age groups. The 2 groups were further stratified on the basis of clinical stage at diagnosis, ethnicity (Asian American, African American, Hispanic, or Caucasian), and histologic type. An additional classification was derived from the previously mentioned ethnic groups that stratified the subjects into 2 groups, Caucasian and minority. Survival was truncated at 60 months and adjusted for disease-specific survival to control for death from other causes not related to cervical cancer.

Analysis. Statistical methods included Cox regression, Kaplan-Meier, and χ^2 analyses with the Statistical Analysis Systems statistical software.[7] A value of $P < .05$ was considered to be statistically significant with the use of 2-tailed tests. We tested the hypothesis of no difference in survival time by the generalized Wilcoxon log rank test.

Results

A total of 3686 women were diagnosed with cervical cancer between 1988 and 1990 inclusively. Among these women 2138 fell within the age groups of interest. One hundred thirty-eight subjects (6%) were excluded because stage was not reported. The final study group of interest consisted of 2000 subjects. The distribution of subjects over the 4 stages is as follows: stage I, 1332 (66.6%); stage II, 272 (13.6%); stage III, 261 (13%); and stage IV, 135 (6.8%). A comparison of the characteristics of the subjects in the 2 age cohorts is presented in Table I.

The mean ages of the patients in groups 1 and 2 were 33 and 48 years, respectively. The younger age group was more likely to have earlier-stage disease ($P = .001$). This distribution held for all ethnic groups ($P < .0001$) except Asian Americans. There was no significant difference in the distribution of tumor grades between the 2 cohorts for each stage. There was no difference in the grade distribution between squamous cell carcinomas and adenocarcinomas, and the distribution of these 2 histologic types was the same among the ethnic groups. However, the older cohort of patients was significantly more likely than their younger counterparts to have adenocarcinoma of the cervix ($P < .005$).

When the 5-year survival was adjusted for cause of death from cervical cancer, the difference between the older and younger cohort was not statistically significant. Cox proportional hazard analysis that included age group, race, histologic type of tumor, stage of tumor, and tumor grade demonstrated no survival advantage or disadvantage to the younger in comparison with the older cohort ($P = .67$, 95% confidence interval 0.74-1.22).

Ethnicity exerted the greatest influence on 5-year survival. By Kaplan-Meier analysis, the Hispanic and Caucasian subjects in the younger cohort had statistically significantly better 5-year survival than their older cohorts ($P < .01$). This finding must be tempered by the fact

that subjects from these ethnicities were more likely to have stage I disease ($P = .001$). Kaplan-Meier analysis within the age cohorts revealed a survival advantage only among the older Caucasian patients with stage I cervical cancer. When analysis was restricted to stage II to IV cervical cancer, this advantage was no longer observed. African American subjects demonstrated a survival disadvantage in comparison with Caucasians (relative risk 1.37, $P = .02$) (Table II). When the model was restricted to race categorized as Caucasian or as minority, the difference in survival was not statistically significant (data not shown). The statistical significance of the other variables in the model was not altered.

Comment

The utilization of this large population-based database and the examination of outcome over a recent period facilitate generalizability and applicability of our findings to present-day treatment recommendations. Other authors have analyzed the influence of age on outcome in cervical cancer. In a hospital-based analysis, Rutledge et al[8] reported a worse outcome among 250 women in whom cervical cancer was diagnosed when they were <35 years old compared with women >35 years old and noted an interaction between young age and disease stage by hazard analysis with adjustment for non–cervical cancer causes of death. A population-based retrospective analysis was performed by Meanwell et al[3] of 10,022 cervical cancer cases between 1951-1981 in England and Wales. A significant favorable survival advantage was noted among the younger cohort of women (<40 years old) when compared with the older cohort (>40 years old). There was no adjustment for cause of death, and the observation period spanned several decades. Unfortunately, patients were treated by heterogeneous modalities at different stages over the study period.

Our analysis of an internationally recognized population-based database indicates that the diagnosis of invasive cervical cancer does not portend a worse prognosis for young women. The diagnosis of earlier-stage tumors among younger women in this analysis was not unexpected, because these women were subjected to the routine cervical cancer screening common in the reproductive period. The lack of similar results among Asian American subjects may be representative of a reluctance of this group to receive routine surveillance. In addition, older patients had a greater time for disease to progress to an advanced stage. When subjects were stratified by disease stage, the difference in grade distribution was not statistically significant between the 2 cohorts. Grade was a significant prognostic factor only for those with grade 4 tumors. This finding must be interpreted with caution because there were only 35 grade 4 cases. Other tumor grades did not serve as prognostic factors, a finding that is consistent with previous reports that grade is not significant in cervical cancer outcome.[9] This population-based analysis did not identify any effect of age on outcome and is consistent with our previous findings in non-population-based studies.[10, 11]

A limitation of this study design is that it does not permit a uniform systematic review of histologic type and grade that may affect the significance of this association. Another factor that must be considered is that, on the basis of the extremes (IA_1 to IB_2), the survival outcome in patients with stage I disease is clearly heterogeneous. Within this database the patients with stage I disease are not easily subdivided, and analysis could not be more specific. If the stage I cases are entirely removed from analysis, the overall survival outcome between the two cohorts remains unchanged.

Prognostic factors such as lymphovascular space invasion and metastatic nodal disease could not be reliably extracted for interpretation. The absence of categorization of these variables does not permit examination of the pattern of spread of disease between the 2 age cohorts. Differences in lymphovascular space invasion and nodal spread are unlikely to alter our interpretation of the data.

The overall perception of a worse outcome among young women with cervical cancer is probably influenced by the greater sense of loss sometimes associated with the poor outcome in a young person. An observation that deserves further analysis is the effect of ethnicity on disease stage and survival among women. In conclusion, these data exclude youth as a significant prognostic factor in the outcome of patients with cervical cancer regardless of disease stage and other known prognostic factors.

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