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Lifestyle modification in cervical cancer survivors: an ongoing need

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Abstract

Objective—With the introduction of multimodality therapy for cervical cancer, many women will be long-term survivors in need of comprehensive surveillance care. Our goal was to evaluate patterns of obesity and smoking in a cohort of cervical cancer survivors, and to assess the potential influence of these comorbidities on subsequent follow-up.

Methods—We reviewed the records of patients treated for invasive cervical cancer at our institution from 2000–2003 who had no evidence of disease ≥ 3 years. Demographic and clinical data were collected, including smoking history and anthropometric measurements. Body mass index (BMI) was categorized according to World Health Organization criteria. Logistic regression, Wilcoxon rank sum, and chi-square analyses were performed.

Results—298 women had complete follow-up data at three years. The median age at diagnosis was 43.5 years (range 17.6–87.1). At diagnosis, 31.9% had a normal BMI, 28.2% were overweight, and 34.6% were obese compared with 31.7%, 21.1%, and 30.2% at 3 years, respectively. Of the 51 women whose BMI categorization changed, 33 (64.7%) had weight gain, and 18 (35.3%) had weight loss. By paired analyses, increase in BMI was significant over the three-year interval ($p<0.001$). Seventy (70) patients actively smoked at diagnosis. Compared with nonsmokers, current smokers had a greater odds of referral to the pain service [OR6.56, CI 6.26–16.43, $p<0.001$], physical therapy [OR 4.74, CI 1.29–17.36, $p=0.02$], and gastroenterology [OR 2.25, CI 1.14–4.24, $p=0.02$].

Conclusion—Obesity and smoking are significant comorbidities which may complicate care in cervical cancer survivors. Interventions aimed at modifying these risk factors should be routinely undertaken in this population.

Keywords

obesity; cervical cancer; smoking

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Conflict of Interest Statement
The authors report no conflict of interest.

Introduction

In 2012, it was estimated that there were 7.2 million female cancer survivors in the United States, over 14% of whom were survivors of gynecologic malignancies [1]. With growing numbers of cancer survivors expected in the next decade, it is important to identify issues which significantly impact their continued health maintenance. Cheung et al [2] acknowledged this fact when they recently reviewed four areas necessary for survivorship care: 1) surveillance of the most recent cancer; 2) screening for cancers other than the primary malignancy; 3) general preventive health; 4) management of other comorbidities. In non-gynecologic tumors, it has been noted that conditions such as obesity, the metabolic syndrome, cardiovascular disease, and osteoporosis continue to plague patients, contribute to deterioration of health, and, in some cases, promote recurrence of disease [3]. A recent review specifically evaluated the impact of lifestyle factors on cancer survivors, highlighting the detrimental effects of obesity and smoking on cancer recurrence and overall survival in studies of patients with breast, prostate, and colon cancers [4].

Cervical cancer affects more than 12,000 women annually in the United States [5]. With the introduction of multimodality treatment, namely concomitant chemoradiation, survival from this disease has significantly improved in the last two decades. As women with cervical cancer transition into the survivorship phase of the cancer continuum, they will require not only surveillance for cancer recurrence and post-treatment sequelae, but also standard health care maintenance. The objective of the current study was to identify the prevalence of smoking and obesity among a cohort of long-term cervical cancer survivors and investigate if these factors influence patterns of subspecialty referral. Such information could not only increase health practitioner awareness of the special needs of this population, but also suggest areas where preemptive health interventions may be of benefit.

Methods

After approval from The University of Texas MD Anderson Cancer Center Institutional Review Board, 365 patients diagnosed and treated at MD Anderson Cancer Center with invasive carcinoma of the cervix between 2000 and 2003 were identified, and their medical records reviewed by a single data abstracter. Random audits were performed by a second independent reviewer to confirm accuracy. Patients with all histologies of cervical carcinoma who had survived disease-free for three years beyond the date of treatment conclusion, and therefore considered long-term survivors, were included. All patients were required to have received definitive treatment with surgery, chemotherapy, radiation, or any combination thereof. Patients who experienced disease recurrence were excluded from the cohort.

Demographic data abstracted included age at diagnosis, race, marital status, and highest level of education achieved. Race was classified as non-Hispanic White, African American, Hispanic, or Asian/other. Marital status was categorized as married, divorced, widowed, separated, or other, and highest level of education as $<8^{th}$ grade, $9–11^{th}$ grade, high school/GED, associate/vocational degree, bachelor degree, or advanced degree. Anthropometric

measurements obtained at patient clinic visits were recorded and body mass indices calculated. The World Health Organization criteria were used to classify patients based upon BMI (BMI<18.5 was classified as underweight; BMI ≥ 18.5 and < 25 was classified as normal weight; BMI ≥ 25 and < 30 was classified as overweight; and BMI ≥ 30 was classified as obese) [6]. Body mass index measurements recorded at the time of diagnosis and three years following completion of treatment were used for comparison. Smoking history at the time of diagnosis was obtained from standardized medical history forms completed by all new patients at our institution, with patients categorized as never smokers, former smokers, or current smokers. Data on subsequent smoking habits were abstracted from clinic notes at any time during the survivorship period through October, 2013.

Data on subspecialty referral patterns were also abstracted. Specifically, patients were classified as 1) not receiving a referral; 2) having a referral discussed with them without a formal consultation request made; or 3) undergoing full consultation by a subspecialist outside the field of gynecologic oncology. Referrals to cardiology, endocrinology, neurology, pain management, physical therapy, orthopedics, nutrition, psychiatry, gastroenterology, urology, and the smoking cessation clinic were tallied.

Statistical analyses were performed using STATA 10.0 (StataCorp, College Station, TX) and SPSS 17.0 (Chicago, IL). Summary statistics were generated to describe the entire patient cohort. The Mann-Whitney and Wilcoxon Signed Ranks tests were used to compare group differences in continuous variables. Logistic regression was used to identify the associations between categorical variables. All tests were two-sided, and p-values <0.05 were considered statistically significant.

Results

Three-hundred sixty-five (365) patients had available data for evaluation. Of these, 298 met inclusion criteria; the remaining 67 experienced disease recurrence and therefore were excluded from the analysis. Patient demographics are shown in Table 1. Consistent with the population at our institution, the greatest proportion of patients was White, non-Hispanic. The majority of patients had early stage disease (FIGO stage 1A1 through stage IB1), and the most commonly employed treatment modality was chemoradiation. Nearly 45% of patients were either current smokers or had formerly smoked.

At diagnosis, the proportions of women who were normal weight (BMI 18.5 to <25 kg/m^2), overweight (BMI ≥ 25 to <30 kg/m^2), and obese (BMI ≥ 30 kg/m^2) were 31.9%, 28.2%, and 34.6%, respectively. At three years from diagnosis, anthropometric data were available for 199 patients. Of these, 31.7% of the patients were normal weight, but only 21.1% were overweight, and 30.2% met criteria for designation as obese. Fifty-one (51) women had changes in their BMI categorization over the time interval. Of these, 33 (64.7%) experienced weight gain, whereas 18 (35.3%) had weight loss. For all patients, the overall median BMI at diagnosis was 27.2 kg/m^2 (range 16.4 to 55.5, SD 7.5). At three years post-treatment, the median BMI was 29.1 kg/m^2 (range 13.7 to 56.1, SD 8.1). Although there was no statistical difference in the group median BMI (p=0.11) between diagnosis and three years post-treatment, by paired analyses, the increase in BMI for all patients over the three-year

interval was statistically significant (p<0.001). Of the 103 women who were obese at the start of treatment, only 15 (14.6%) were referred to a nutritionist for dietary counseling at some point during active treatment or follow-up.

Seventy (70) patients actively smoked at the time of diagnosis; sixty-four were former smokers. Smoking cessation and referral to the tobacco cessation clinic on site were discussed with 34 active smokers at some point during treatment or follow-up (48.6%). Of these, only four (11.8%) accepted referral; none of these patients stopped smoking. In the cohort of active smokers for whom follow-up smoking habits were documented, 15 (21%) quit smoking during treatment or follow-up. Only 5 of these patients had been counseled about smoking cessation. Thirty-two patients (46%) continued to smoke throughout the duration of their follow-up.

Univariate logistic regression analyses were performed to assess associations between increasing body mass index, smoking history, and subspecialty referrals (Table 2). Compared to patients of normal weight, patients with body mass indices qualifying them as overweight or obese did not have a statistically significant greater likelihood of referral to any specialty or consultation service. However, referral patterns were significantly related to a patient's smoking history. Compared to patients who had never smoked, current and former smokers as a group were more likely to have been referred to pain management (OR 6.56; 95%CI [2.62, 16.43]; p<0.001), physical therapy (OR 4.74; 95%CI [1.29, 17.36]; p=.02); gastroenterology (OR 2.25 [CI 1.14–4.24], p=0.02). The data also suggested that patients who were current and former smokers were also more likely to have referrals to psychiatry but this was not statistically significant (OR 1.84; 95%CI [0.95, 3.53]; p=0.07). Similarly, current and former smokers were more likely to have gastroenterology referrals (OR 1.45; 95%CI [0.89, 2.37]; p=0.14). Further classification of smoking status shows distinct differences in odds of referral. Table 2 shows the odds ratios when patients were classified as never having smoked ("never"), smoking at the time of diagnosis ("current"), or having smoked in the past but no longer smoking at the time of diagnosis ("former"). Compared to patients who had never smoked, patients who were current smokers were the most likely to receive referrals to the pain management service (OR 9.69; 95% CI [3.67, 25.57]; p<.001) and psychiatry (OR 2.37; 95%CI [1.13, 4.98]; p=.02). The same trend was noted for physical therapy (OR 4.08; 95%CI [0.95, 17.56]; p=.06) and gastroenterology (OR 1.75; 95%CI [0.99, 3.20]; p=.05), although these narrowly missed achieving statistical significance.

Discussion

Improvements in cancer treatment strategies have allowed oncologists to positively affect survival outcomes of their patients. As such, the population of cancer survivors continues to grow exponentially. Screening for secondary malignancies, optimizing the management of other medical comorbidities, and implementing lifestyle changes aimed at promoting both physical and mental well-being must be a standard part of care for the cancer survivor. While surveillance for recurrent disease is important, so too is an awareness of overall patient health. In this study, we identified two areas where active intervention both during and after treatment for malignancy is necessary for cervical cancer survivors: obesity and

smoking. The survivors in this study population had significant weight gain during the three years immediately following treatment, and those who were smokers had greater referral to subspecialists. Addressing weight loss and smoking habits in this group of patients, therefore, is essential.

Obesity is a growing epidemic in the United States, and our data suggest that cervical cancer survivors are at risk for gaining weight post-treatment. This is significant as obesity has been associated with cervical cancer mortality in the general population [7]. It has been suggested that inflammatory mediators in adipose tissue may predispose to altered cancer biology and disease promotion [8]. Beyond just cancer survival, though, implementing diet and exercise programs for these women is also important to prevent obesity-associated sequelae, such as hypertension and diabetes, which are frequently overlooked in cancer survivors [9]. Strategies to reduce obesity by diet modification and increasing physical activity in cancer survivors have demonstrated positive results. Scott et al [10] implemented a diet and exercise program in a cohort of breast cancer survivors, and noted reductions in waist/hip ratio, waist circumference, total cholesterol, and resting blood pressure. Quality of life was also significantly improved. The implementation of physical activity programs as part of the survivorship plan has also been shown to be beneficial in colorectal cancer, with reduced fatigue, improved aerobic capacity, and positive emotional well-being [11].

Smoking has long been known to complicate treatment in patients receiving chemoradiation for cervical carcinoma. Eifel et al [12] published a large series of 3489 patients treated with definitive radiation for invasive cervical cancer. In their series, smoking ≥ 1 pack of cigarettes daily translated into an increase in late complications involving the bladder, rectum, and small bowel. In fact, more than 5% of smokers experienced some sort of late rectal complication. Our finding that there was a substantial increase in referrals to gastroenterology in the subset of patients who smoked may be explained by the long-term effects of smoking in radiated tissue.

Smokers had a greater likelihood of referral to pain management specialists and psychiatrists in this study, and there is substantial data describing a relationship between smoking and pain. Daniel et al [13] noted in a cohort of 893 lung cancer patients that increased nicotine intake was related to a greater perception of pain. In fact, a larger proportion of persistent smokers reported moderate to severe pain at any time during treatment than nonsmokers or former smokers. A similar study published by Ditre et al [14] of patients with multiple different types of cancers reported that continued smoking during and after treatment was associated with greater pain severity and interference from pain. The relationship between smoking, pain, and psychiatric symptoms is even more complex. To date there are no good data to adequately define a causal relationship between the three, though observed associations have been reported [15].

Though the negative effects of smoking in both survivors and patients with active cancer are well documented, there is still hesitation on the part of the providers to inquire about smoking and engage patients in aggressive smoking cessation efforts. In our cohort, less than 50% of patients had smoking cessation discussed with them, despite the abundance of resources available to assistant in tobacco cessation efforts, including counseling and

pharmacologic therapies. Weaver et al [16] recently surveyed a cohort of oncologists about tobacco cessation strategies and reported that 82.4 % of oncologists reported assessing smoking at initial patient visits, but very few consistently asked about tobacco use at subsequent visits. Despite this finding, only 18.1% of providers reported high levels of confidence in their ability to counsel smoking patients, citing lack of referral services or lack of training as important barriers to counseling. While the population in this cohort was small (n=111), subsequent authors have noted similar findings [17].

This is a retrospective review, and as such is subject to the biases associated with its design. As a tertiary care center, many patients were sent to community providers for concurrent medical management during their cancer surveillance, so follow-up recommendations from consultants with subsequent outcomes were not available for review. In addition, missing data, including ongoing changes in smoking habits, may not be available for capture. However, this is the largest series to date to specifically compare biophysical and smoking trends in a population of cervical cancer patients. These data are timely because they suggest two areas where aggressive interventions in the cervical cancer survivor population may have substantial benefit. With a large number of resources available to physicians and patients to assist with smoking cessation, dietary changes, and initiating exercise programs, neglecting to actively modify such important, yet underappreciated, components in patients' lives could prove to be a detriment to women who have already met the challenges of cancer treatment.

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Table 1

Patient Demographics (n=298)

Age at diagnosis, years (median/range)	43.5 (17.6, 87.1)
Characteristic	Number (%)
Race	
White, non-Hispanic	164 (55.0)
African American	36 (12.1)
Hispanic	90 (30.2)
Asian/other	8 (2.7)
Stage	
IA1 + IA2	32 (10.7)
IB1 + IB2	172 (57.7)
II	59 (19.8)
III + IV	35 (11.7)
Treatment Modality	
Primary Surgery	48 (16)
Primary Chemotherapy/Radiation	250 (84)
Highest Education Achieved	
Less than 8^{th} grade	20 (6.7)
9^{th} – 11^{th} grade	25 (8.3)
High school/GED	48 (16.1)
Associates/Vocational degree	45 (15.1)
Bachelor's degree	39 (13.1)
Advanced degree	12 (4.0)
Not available	109 (36.7)
Marital Status	
Single	58 (19.5)
Divorced	32 (10.7)
Widowed	26 (8.7)
Married	174 (58.4)
Other	8 (2.7)
Smoking Status at diagnosis *1*	
Never smoker	162 (54.4)
Current smoker	70 (23.5)
Former smoker	64 (21.5)
BMI at diagnosis *2*	
Normal (18.5 to <25 kg/m^2)	95 (31.9%)
Overweight (25 to <30 kg/m^2)	84 (28.2%)
Obese (BMI ≥ 30 kg/m^2)	103 (34.6%)

Underweight (<18.5 kg/m^2)	11 (3.7%)

[1] Smoking data missing for 2 patients

[2] BMI data missing for 5 patients

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Table 2

Univariate associations between BMI classification and smoking status and subspecialty referral.

		Cardiology			Endocrinology			Neurology		
	n	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
BMI				1.00			0.74			0.99
Normal (ref)	95	-	-	-	-	-	-	-	-	-
Overweight	84	1.14	0.38, 3.40	0.81	0.54	0.15, 1.88	0.34	1.00	0.37, 2.74	0.99
Obese	103	1.06	0.37, 3.04	0.92	1.04	0.39, 2.82	0.94	1.14	0.45, 2.89	0.78
Underweight	11	0.00	0.000, -	0.99	1.09	0.12, 9.62	0.94	0.96	0.11, 8.35	0.97
Smoking				0.89			0.47			0.68
Never (ref)	162	-	-	-	-	-	-	-	-	-
Current	64	1.29	0.46, 3.63	0.63	0.83	0.26, 2.71	0.76	1.18	0.45, 3.05	0.74
Former	70	1.16	0.39, 3.49	0.79	1.69	0.62, 4.56	0.30	1.51	0.60, 3.80	0.38

		Pain Management			Physical Therapy			Orthopedics		
	n	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
BMI				0.18			0.92			0.68
Normal (ref)	95	-	-	-	-	-	-	-	-	-
Overweight	84	2.00	0.67, 5.77	0.19	0.67	0.15, 2.88	0.59	0.90	0.34, 2.38	0.82
Obese	103	1.96	0.70, 5.44	0.19	1.11	0.33, 3.78	0.86	0.53	0.18, 1.51	0.23
Underweight	11	5.56	1.17, 26.6	0.03	0.00	0.000, -	1.0	0.00	0.00, -	1.00
Smoking				<.000			0.06			0.59
Never (ref)	162	-	-	-	-	-	-	-	-	-
Current	64	9.69	3.67, 25.57	<.001	4.08	0.95, 17.56	0.06	1.28	0.46, 3.63	0.63
Former	70	3.71	1.23, 11.18	0.02	5.48	1.33, 22.64	0.02	1.69	0.62, 4.56	0.30

		Nutrition			Psychiatry			Gastroenterology		
	n	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
BMI				0.62			0.40			0.82
Normal (ref)	95	-	-	-	-	-	-	-	-	-

	Nutrition				Psychiatry			Gastroenterology		
	n	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Overweight	84	1.06	0.47, 2.40	0.89	0.48	0.20, 1.19	0.11	1.26	0.67, 2.38	0.48
Obese	103	1.48	0.71, 3.11	0.30	0.97	0.47, 2.02	0.94	1.30	0.71, 2.37	0.40
Underweight	11	0.58	0.07, 4.88	0.62	0.00	0.00, -	1.00	1.44	0.39, 5.32	0.59
Smoking				0.68			0.07			0.15
Never (ref)	162	-	-	-	-	-	-	-	-	-
Current	64	1.31	0.62, 2.76	0.47	2.37	1.13, 4.98	0.02	1.78	0.99, 3.20	0.05
Former	70	1.33	0.62, 2.85	0.47	1.31	0.56, 3.09	0.54	1.15	0.61, 2.15	0.67

	Urology			
	n	**OR**	**95% CI**	***p***
BMI				0.15
Normal (ref)	95	-	-	-
Overweight	84	2.00	0.85, 4.69	0.11
Obese	103	2.44	1.10, 5.45	0.03
Underweight	11	0.85	0.10, 7.35	0.88
Smoking				0.31
Never (ref)	162	-	-	-
Former	64	1.51	0.73, 3.15	0.27
Current	70	1.69	0.81, 3.54	0.16