

Marital Status and the Incidence of Sarcomas of the Uterus¹

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ABSTRACT

To explore further the descriptive epidemiology of sarcomas of the uterus, we examined the distribution of marital status among 1479 white women diagnosed as having one of these tumors between January 1, 1973, and December 31, 1986, in 7 geographically defined areas of the United States. We estimated incidence rates based on the distribution of marital status of the female population of these seven areas as of 1980; adjustment for the prevalence of intact uteri in the estimated population-at-risk was performed using data from a survey of a representative sample of the United States population in 1982-1984. The incidence of uterine sarcoma was higher among never-married compared to ever-married women (rate ratio, 1.5; 95% confidence intervals, 1.3, 1.8). The association with marital status was similar for each of the three major histological categories (leiomyosarcomas, malignant mixed müllerian tumors, and endometrial stromal sarcomas). These results provide evidence that one or more characteristics associated with a woman's marital status may play a role in the etiology of one or more histological types of uterine sarcoma.

INTRODUCTION

Sarcomas of the uterus are rare tumors with a largely unexplored and consequently unknown etiology. The incidence of these neoplasms appears to be higher among blacks than among whites (1) and may also be increased among women who have received therapeutic ionizing radiation for cervical cancer or benign gynecological disorders (2, 3). No other risk factors have been described. On the basis of the age-specific incidence of the different histological types of uterine sarcoma, Harlow *et al.* (1) proposed that leiomyosarcomas, as opposed to malignant mixed müllerian tumors and endometrial stromal sarcomas, may share etiological factors with epithelial tumors of the breast, ovary, and endometrium. If this were true, it might be expected that the pattern of incidence of leiomyosarcoma of the uterus resembles those of carcinoma of the breast, ovary, and endometrium with respect to characteristics other than age. One feature of the epidemiology of these more common malignancies is that they occur with greater frequency among never-married than among ever-married women (4, 5). To determine whether the occurrence of uterine sarcomas differs by marital status in a manner similar to that previously observed for other reproductive neoplasms and, if so, whether or not such an association varies by the histological type of uterine sarcoma, we analyzed the incidence of these tumors among women of different marital status using data from the network of population-based cancer registries comprising the SEER³ program.

MATERIALS AND METHODS

The nature and operation of the SEER program have been described elsewhere (6). There were 1562 women 25 years of age or older

diagnosed with sarcoma of the uterine corpus, uterine cervix, or uterus, not otherwise specified, between January 1, 1973, and December 31, 1986, among white residents of the following geographic areas served by population-based cancer registries participating in the SEER program during the majority of this time period: the States of Connecticut, Hawaii, Iowa, New Mexico, and Utah; and the metropolitan areas of San Francisco-Oakland and Seattle-Puget Sound (since January 1, 1974). Although SEER registries serving the Atlanta and Detroit metropolitan areas also were in operation during this period, we excluded cases diagnosed in these regions because population estimates classified by marital status and age (see below) are not published for the specific counties covered by the respective surveillance systems. We restricted our analyses to white women because the majority of tumors reported among blacks would have been diagnosed among residents in the two geographic areas which had to be excluded from our analysis.

Marital status at diagnosis is routinely recorded by SEER registries from information available in the medical records abstracted for each case, and is classified as single (never married), currently married, widowed, separated, divorced, and unknown. Separated and divorced women were aggregated for this analysis because of the small number of cases in each of these two categories. We excluded 29 tumors diagnosed in women for whom marital status was unknown and 10 tumors for which the diagnosis was either not confirmed microscopically or made only at autopsy.

Based on pathology reports reviewed by trained personnel at each registry, tumors reported to the SEER program are classified by histological type according to the first four digits of the *International Classification of Diseases for Oncology* (ICD-O) morphology code (7). We further aggregated the tumors as: leiomyosarcomas (ICD-O M:8890-8891); endometrial stromal sarcomas (ICD-O M:8930); malignant mixed müllerian tumors (ICD-O M:8933, 8950-8951, 8940, 8960, 8980-8981); and sarcomas, not otherwise classified (ICD-O M:8800-8801). These categories accounted for over 97% of the uterine sarcomas diagnosed during the study period; the remaining 44 tumors were excluded, leaving 1479 cases for analysis.

In order to study whether any association observed between the occurrence of uterine sarcomas and marital status is specific to soft tissue tumors of the uterus, we also examined the incidence of sarcomas arising outside of the uterus and diagnosed during the study period among white women living in the same seven geographic areas listed above. Of the 8450 nonuterine sarcomas reported, we excluded 755 cases that were diagnosed in women with unknown marital status, were not microscopically confirmed, or were diagnosed only at autopsy. We also excluded 6730 cases that were not coded as leiomyosarcomas or malignant mixed müllerian tumors, the morphological variants which comprise the majority of uterine sarcomas. As a result, 965 sarcomas coded as originating outside of the uterus (602 leiomyosarcomas and 363 malignant mixed müllerian tumors) were included in the analysis.

From published reports of the United States Bureau of the Census, we obtained estimates of the 1980 white female population of each of the geographic areas served by the seven SEER registries providing data for this analysis, classified by age (25-29 years, . . . , 50-54 years, 55-64 years, 65-74 years, and 75+ years) and marital status (8). The classification of marital status in the Bureau of the Census data is identical to that in the SEER program, although the information is obtained through self-report. The Bureau of Census estimates for 1980 were multiplied by a constant equal to the number of years that a particular SEER registry contributed cases during the study period.

Analyses of rates of uterine neoplasms among subgroups of a population can yield erroneous results if there are important differences in the rates of hysterectomy among the groups being compared (9). To account for the prevalence of intact uteri in our study population, which in all likelihood would vary by both marital status and age (10, 11), we

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³ The abbreviations used are: SEER, Surveillance, Epidemiology, and End Results; NHANES I-EFS, National Health and Nutrition Examination Survey I-Epidemiological Followup Survey; CI, confidence interval.

adjusted the population estimates described above using data obtained from the NHANES I-EFS (12, 13). The NHANES I-EFS ascertained information on age, current marital status, and presence of intact uteri from a nationally representative sample of 5581 white women 30 years of age and older in 1982–1984. The age and marital status-specific proportions of that study population with intact uteri were calculated incorporating the complex sampling design of the cohort, yielding estimates applicable to the United States white female population (due to the lack of information on 25–29-year-old females in the NHANES I-EFS data, we assumed that 100% of these women, regardless of marital status, had an intact uterus). These percentages were then multiplied by the corresponding population figures from the Census Bureau to obtain an estimate of the true population-at-risk. Age-adjusted incidence rates by marital status and histological type were calculated by the direct method, using the age-specific 1980 United States female population estimates as the weights for standardization (14, 15). Ninety-five% CI on the ratio of age-adjusted rates were computed for comparisons of the incidence of uterine sarcoma among never-married women to that among ever-married women (16).

RESULTS

The average annual age-adjusted incidence of all histological types of uterine sarcoma combined was 50% higher among women who had never been married compared to women who had ever been married (58.6 *versus* 38.0/million women with intact uteri). Table 1 shows the incidence of the major histological types of uterine sarcoma among never-married and ever-married women. The incidence of each type was higher in never-than in ever-married women, with little variation among types. There were too few cases of sarcoma, not otherwise specified, diagnosed among never-married women to permit separate analyses. In general, the incidence of each histological type of uterine sarcoma was higher among never-married women than ever-married women regardless of whether the latter were currently married, separated or divorced, or widowed (Table 2). Widowed and divorced or separated women tended to have lower and higher rates, respectively, than did currently married women.

When stratified by age, the association of marital status with the incidence of all histological types of uterine sarcoma combined was strongest among women 45–54 years of age at diagnosis (rate ratio, 1.9) and absent or weaker among the younger (rate ratio, 0.9) and older women (rate ratio, 1.3), respectively.

The age-adjusted incidence of leiomyosarcoma arising outside of the uterus was slightly higher among never-married women compared to ever-married women (13.2 *versus* 10.8/million women with intact uteri per year; rate ratio, 1.2; 95% CI, 0.9, 1.7), while the incidence of nonuterine malignant mixed müllerian tumors was twice as high among never-married

Table 2. Incidence^a of sarcoma of the uterus, by histological type and detailed marital status, whites, Seven Surveillance, Epidemiology, and End Results Program Registries, 1973–1986

Histological type	Marital status			
	Never married	Currently married	Separated/divorced	Widowed
Leiomyosarcoma	18.4 (41) ^b	14.9 (363)	14.4 (48)	13.2 (73)
Malignant mixed müllerian tumors	32.3 (77)	21.7 (383)	34.1 (78)	14.8 (212)
Endometrial stromal sarcoma	5.9 (16)	4.0 (90)	6.2 (18)	2.4 (29)
All types ^c	58.6 (138)	42.2 (870)	55.3 (146)	31.4 (325)

^a Average annual rate per million women with intact uteri age 25 years or older, adjusted to the age distribution of the 1980 United States female population.

^b Numbers in parentheses are number of cases.

^c Includes sarcomas, not otherwise classified.

women as among ever-married women (12.4 *versus* 6.2/million women with intact uteri per year; rate ratio, 2.0; 95% CI, 1.4, 2.8).

DISCUSSION

Several limitations must be considered when evaluating the validity of our results. We attempted to reduce the effect of bias that might arise from variation in the rate of hysterectomy among women of different marital status (10, 11) by adjusting our population estimates using data on the prevalence of intact uteri from a nationally representative sample of women. Ideally, we would have preferred to perform such an adjustment with similar data obtained from the populations of the seven geographic areas under study, but such information is not available for the age range of women in our analysis. To the extent that the white female population of the seven SEER areas differs from that of all United States white women with respect to the age- and marital status-specific prevalence of intact uteri, our results will be incorrect. In addition, some of the estimates of the prevalence of intact uteri used to adjust the United States Census population figures are based on relatively few women in the NHANES I-EFS survey. Thus, even if national data are applicable to our study population, sampling errors could have led to some over- or underadjustment for the prevalence of intact uteri.

A potential source of incomparability between the numerator and denominator data in our analysis is that the distribution of marital status of the study population was based on a single year and was assumed to be constant throughout the 14-year period during which the cases of uterine sarcoma were ascertained. If such an approach selectively underestimates the population of never-married women (due to major changes in the size of the never-married population during the study period), falsely increased risks among never-married women would have been produced. However, data from the Census Bureau indicate that between 1973 and 1986 the proportion of all United States women who had never been married changed only slightly (approximately a 2% increase) (17), so that it is unlikely that this aspect of our estimated population-at-risk has led to any appreciable degree of bias. We have no information on the relative accuracy of the classification of marital status in the United States Census and SEER data, but it might be expected that since the latter is based on review of medical records, rather than self-report, there would be greater potential for misclassification of marital status among the cases than the population estimates. If this is true, the associations with having never been married that we observed might be somewhat overestimated if there was a tendency for cases who were single (sepa-

Table 1. Incidence^a of sarcoma of the uterus, by histological type and marital status, whites, Seven Surveillance, Epidemiology, and End Results Program Registries, 1973–1986

Histological type	Marital status		Rate ratio ^b	95% CI
	Never-married	Ever-married		
Leiomyosarcoma	18.4 (41) ^c	13.5 (484)	1.4	1.0, 1.9
Malignant mixed müllerian tumors	32.3 (77)	19.5 (673)	1.7	1.3, 2.2
Endometrial stromal sarcoma	5.9 (16)	3.8 (137)	1.5	0.9, 2.7
All types ^d	58.6 (138)	38.0 (1341)	1.5	1.3, 1.8

^a Average annual rate per million women with intact uteri age 25 years or older, adjusted to the age distribution of the 1980 United States female population.

^b Ratio of incidence among never-married women relative to incidence among ever-married women.

^c Numbers in parentheses are number of cases.

^d Includes sarcomas, not otherwise classified.

rated, divorced, or widowed) at the time of diagnosis to be erroneously recorded as "single, never married" by tumor registry abstractors.

The distinction among morphological types of uterine sarcoma, as well as between these malignancies and their benign counterparts, is often not straightforward. High grade leiomyosarcomas or malignant mixed müllerian tumors may be misclassified as sarcomas, not otherwise specified (or *vice versa*) (18, 19). In addition, some tumors coded as leiomyosarcoma in fact may be leiomyomas which were misclassified on the basis of variation in the number of mitoses counted per high-power field (19, 20). We were unable to review the histological diagnoses of the cases analyzed in this study; thus our results may have been influenced by the varying diagnostic criteria used by pathologists practicing in the seven geographic areas from which data were obtained. Although we cannot rule out the possibility that the accuracy of diagnosis of one or more histological types of uterine sarcoma depends to some degree upon a woman's marital status, we are unaware of any evidence suggesting that any misclassification present would not be similar for never-married and ever-married women. Thus, for any particular histological type of uterine sarcoma, we believe that errors in classification would most likely have led to rate ratios which are, if anything, attenuated relative to the true associations with marital status; indeed, there may exist somewhat greater variation than we observed among histological types in the size of the association with marital status, since errors in classification would tend to obscure differences between morphologies of these tumors.

Given that the incidence of carcinomas of the breast, ovary, and endometrium is higher among never-married women (4, 5), the hypothesis that uterine leiomyosarcomas may share etiological factors with these more common neoplasms suggests that if any similar association with marital status exists among the three major histological types of uterine sarcoma, it would be most apparent for leiomyosarcomas. However, our data indicate that the increased risk associated with having never been married differs little among the morphological variants of uterine sarcoma. Although it is possible that the occurrence of all histological types of uterine sarcoma truly varies among ever-married women (Table 2), some of those differences may be due to residual confounding by age, since 10-year age categories were used for standardization over an age range (55 years and older) in which the incidence of uterine sarcoma and the proportion of widowed and separated or divorced women in the population changes greatly. The absence of a more striking contrast in the association of uterine and nonuterine leiomyosarcomas with having never been married is not consistent with the respective patterns of age-specific incidence, which differ markedly (1). That nonuterine malignant mixed müllerian sarcomas exhibited an association with marital status is not surprising, since the majority of these neoplasms arose in the gynecological tract (primarily the ovary and pelvic cavity).

If never-married women truly have a higher incidence of uterine sarcoma than ever-married women, consideration of the characteristics that distinguish never-married and ever-married women might provide insight into factors that play a role in the etiology of these rare neoplasms. The presence of similar associations with marital status among patients with epithelial malignancies of the breast, uterine corpus, and ovary has been interpreted in terms of the lower frequency of prior pregnancy and live births among never-married women (4, 5). At present there are only a few pieces of evidence which bear on whether or not the occurrence of uterine sarcomas is related to either

pregnancy or child-bearing. During pregnancy, the endometrial stroma (the tissue from which malignant mixed müllerian tumors and endometrial stromal sarcomas arise) undergoes decidualization (21). The cellular changes of decidualization are similar to differentiation: thus it might be hypothesized that pregnancy would tend to reduce the propensity for malignant transformation of the stromal tissue. In addition, recent case-control studies have found that uterine leiomyomas develop more often in women who are nulliparous (22, 23). A similar association might exist for leiomyosarcomas, since what little is known about the risk factors for benign and malignant uterine smooth muscle tumors suggests that they have shared epidemiological features [the incidence of both neoplasms peaks in the latter half of the reproductive years and is higher among black women (1, 24)]. Only one very small study has directly examined the role of childbearing on the occurrence of uterine sarcomas, and that investigation reported that parous women were at a slightly higher risk of these tumors than were nulliparous women (25).

Our results provide evidence that women who have never been married are at increased risk for all histological types of uterine sarcoma and therefore do not support the theory that the epidemiology of uterine leiomyosarcoma is more similar to the epidemiology of epithelial tumors of the breast and gynecological tract than is the epidemiology of other uterine sarcomas. Whether or not the association with marital status can be accounted for by the higher prevalence of nulliparity among never-married women, or by any other factor(s), remains to be determined in more detailed epidemiological studies. Given the morphological diversity of these tumors, such investigations should enroll sufficient numbers of subjects to allow separate analyses for the major histological types.

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