editorial

Beyond Obesity: The Rising Incidence and Mortality Rates of Uterine Corpus Cancer

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Uterine corpus cancer (uterine cancer) is one of the few cancers in the United States where incidence continues to increase significantly. This trend has been reported worldwide, particularly in higher-income countries and those undergoing rapid socioeconomic transitions.[1] Estimates of incidence that do not correct for hysterectomy prevalence, such as those reported by the SEER program, rank uterine cancer as the fourth most common cancer among women, after breast, lung, and colorectal cancers.[2] However, once rates are adjusted for the approximately 25% of women without intact uteri who are no longer at risk, uterine cancer becomes the second most commonly diagnosed type of cancer.[3] Recognition of the burden of disease is crucial to direct resources toward awareness, prevention, early detection, and treatment.[4,5]

In the article that accompanies this editorial, Clarke et al[3] present compelling data showing hysterectomy-corrected uterine cancer rates increased approximately 1% per year from 2003 to 2015, with the most rapid increases seen in Hispanic, Asian, and non-Hispanic black (NHB) women, respectively. Additionally, rate increases were greatest for the more aggressive nonendometrioid subtypes (here defined as serous, clear cell, and carcinosarcoma subtypes), which comprise 18.3% of all uterine cancers. These cancers were twice as frequent in NHB women, representing 34.9% of uterine corpus cancers in this population. The poorer prognosis of nonendometrioid cancers partially explains the lower 5-year survival for NHB women overall, but closer analysis revealed that NHB women had worse survival across all stages and subtypes. Past epidemiologic studies have not had sufficient numbers of under-represented minority women to examine factors related to disease risk or survival, particularly for nonendometrioid cancers.[6,7]

A vast majority of epidemiologic research has focused on the most common histologic subtype, low-grade endometrial endometrioid cancer, which has an excellent prognosis, with 5-year relative survival after diagnosis of 97.5%.[2] This impressive survival rate overshadows concerning data that show the overall survival rate has been decreasing over the last several decades, dropping from an 87% 5-year survival rate for diagnoses during 1975 to 1977 to 83% for those during 2008 to 2014.[2] The number of women who die each year in the United States is similar for both ovarian and uterine cancers, with an estimated 12,160 deaths resulting from uterine cancer and 13,980 resulting from ovarian cancers.[2] However, comparatively, the morbidity and mortality associated with uterine cancer remain underacknowledged, underfunded, and ultimately understudied.[4]

The study by Clarke et al[3] suggests that the usual explanation for the rise in uterine cancer incidence (ie, the obesity epidemic) does not explain the sharp rise in aggressive subtypes. In this regard, although excess unopposed estrogen in obese women is a strong risk factor for the development of low-grade endometrioid endometrial cancers, it may play less of a role in the nonendometrioid aggressive subtypes. Given the older median age at diagnosis of nonendometrioid cancers, this increase likely reflects differences in women born on the cusp of the baby boomer generation compared with women who are squarely baby boomers.[8] The latter group had increasing use of oral contraceptives, older ages at first births, and some of the highest smoking adoption rates among women.[9-11] Paradoxically, the decrease in tobacco smoking in the United States may also account for some of the increase in uterine cancer incidence, because current smokers have approximately 50% lower risk for uterine cancer.[6] Of course, given the multitude of cancers and other diseases associated with tobacco smoking, this would never be recommended as a way to curb the rising incidence of uterine corpus cancer. Other factors that could be responsible for the rise include the use of postmenopausal estrogen, nulliparity and changing reproductive patterns (eg, fewer births, earlier age at menarche), and genetic syndromes.[6,12]

Disentangling the complex relationships that underlie the increasing incidence of aggressive endometrial cancers, the higher prevalence of aggressive disease among NHB women, and the racial disparity in survival will be key to identifying effective individual and population-based interventions. This will not be an easy task, but some direction may be gleaned from breast cancer research. The epidemiologic profile of aggressive uterine cancer somewhat mirrors that of triple-negative breast cancer (TNBC). NHB women are twice as likely to develop TNBC compared with non-Hispanic white and Hispanic women, and this is a more aggressive, non–estrogen-based disease with

ASSOCIATED CONTENT

See accompanying article on page 1895

Author affiliations and support information (if applicable) appear at the end of this article.

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much poorer prognosis than estrogen-driven breast cancers.[13,14] Although an African ancestry–related genetic driver for TNBC has been sought, none has been found; moreover, huge genetic variation exists among breast cancers in Africa.[15,16] In addition, women may have experienced stressors that have nothing to do with biologic ancestry. Although genetic ancestry may be a fixed trait, race is a mutable social construction and must be considered distinctly. Often what is represented as a racial effect reflects unmeasured confounding, because racial patterns influence access of certain groups to social and physical environments that in turn alter biology. For example, birth in a Jim Crow state increased the odds of estrogen receptor–negative breast cancer for NHB women but not white women; however, most studies do not consider this racial history in analyses.[17] The best way to capture this unmeasured confounding is to consider the role of social context and history.

The dynamics prevalent throughout history, culture, politics, and economics that disadvantage racial minorities create social patterning of health outcomes.[18] Two potential ways these patterns are being internalized to biology are emerging in life course epidemiology and studies of the microbiome. Given the range of likely birth cohorts reflected in these trends, women were increasingly joining the workforce, which has been associated with stress.[19] Beyond this, NHB women experience social, economic, and political marginalizations that translate into higher allostatic load and weathering on the body.[20] This may result in higher proportions of comorbid conditions, both measured (eg, hypertension) and still unknown. For example, the hypothalamic-pituitary-adrenal axis (HPA) and the hypothalamic-pituitary-gonadal (HPG) axis have a reciprocal relationship. Chronic psychosocial stress activates the HPA, which impedes the HPG, resulting in inhibition of endogenous estrogen production.[21,22] Thus, chronic stress may reduce risk of tumors driven by estrogen, leaving NHB women at risk for aggressive uterine cancer diagnosed at older ages.

Additional evidence that experiences over the life course are critical come from a population-based record-linkage study from Denmark that reported low birth weight was associated with risk of aggressive uterine cancers, although there were a limited number of these cases.[23] Low birth weight is more common among NHB women and Hispanic women, and a large body of evidence suggests weathering or stress as a mechanism.[24-28] Other relevant life course findings, which highlight the interrelatedness of many of factors associated with uterine cancer risk, include reports that lower socioeconomic status during childhood lowers age at menarche, even after adjustment for body mass index.[29] Research that integrates social and biologic factors across the life course, in diverse populations, may provide insight into the increasing rates of uterine cancer.

Lastly, although the microbiome has yet to be explicitly implicated in gynecologic cancers, there are plausible channels for its involvement in carcinogenesis. There is evidence of vaginal microbiome changes associated with pelvic inflammatory disease, intrauterine devices, and human papillomavirus susceptibility, to name a few possibilities.[30] Preliminary work suggests that presence of *Atopobium vaginae* and an uncharacterized *Porphyromonas* species was associated with endometrial cancer in those with a high vaginal pH.[31] Characterization of the vaginal and uterine microbiomes may provide insight into uterine carcinogenesis and ultimately lead to prevention strategies.[32] In line with the stress hypothesis, stress disrupts the vaginal microbiome, which may be passed to offspring during childbirth, disrupting their digestive microbiome, because it is also implicated in GI microbiome changes.[33,34]

The key to uterine cancer control is better understanding of the biology and etiology of uterine cancer, particularly the nonendometrioid cancers that are underlying the rise in uterine cancer incidence and driving mortality. In addition, although advances have been made using immune checkpoint inhibitors for advanced uterine and other cancers exhibiting high levels of microsatellite instability, progress in treating these cancers has generally been slow.[35,36] A multidisciplinary approach considering both the life course and social context in epidemiologic research, coupled with strong clinical efforts to develop new approaches to understand tumor biology and provide targeted treatment, will be necessary to reverse the current trends in incidence and mortality and ultimately achieve health equity.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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