Editorial

The challenging task of uncovering disparities in endometrial cancer

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Over the last fifty years, the incidence of endometrial cancer has risen globally (1). While much of this rise may be attributed to increasing rates of obesity in many nations (2), endometrial cancer actually represents a diversity of histologies, with variable risk factors, genetic susceptibilities, and outcomes. The majority of women diagnosed with endometrial cancer will have low-risk disease, with favorable outcomes; however, certain minority groups are at higher risk for aggressive subtypes and poorer survival (3,4). Black women, for example, have a lower overall incidence of endometrial cancers but have a higher death rate (7.8/100,000) than White women (4.1/100,000) (5). Additionally, black women have a higher likelihood of being diagnosed with a type II, aggressive endometrial histology, and even when matched by treatment algorithm, do more poorly than white women (6). Understanding the differences in the molecular profiles of these tumors, surgical management, and adjuvant treatment approaches between women of different races, ethnicities, and socioeconomics is crucial to optimize care for this disease and diminish observed disparities in outcome.

One such consideration is hospital volume and its impacts on survival. In 2010, Bristow *et al.* reported on hospital case volumes and ovarian cancer survival (7). Their findings suggested that high hospital case volume was modestly associated with improved overall survival, in part due to greater adherence to standard of care therapy. They also found that race, ethnicity, age, and insurance status were also independent predictors of outcome. Others have reported similar findings in breast, esophageal, and pancreatic cancer (8-10). But in other, non-gynecologic cancers, the data on surgical volume and cancer outcome are not definitive. Simunovic *et al.* (11) reported in 2006 that among women with breast cancer, a high-volume center did not translate into a survival benefit compared to centers with moderate volume. Jonker *et al.* (12) similarly reported that among patients with rectal cancer, there was no impact of hospital volume on long-term oncologic outcome.

In April, 2018, Buskwofie *et al.* (13) sought to evaluate the effect of hospital volume on outcomes for endometrial cancer, and to determine if volume affected treatment outcomes in minority black women. Using the National Cancer Database (NCDB), women surgically treated for endometrial cancer with hysterectomy as part of their treatment between 1998 and 2011 were identified. Statistical analyses were done using Cox proportional hazards models, with multiple adjustments. The authors found that black women were more likely to receive care at a high-volume center. High-volume centers were more likely to perform lymphadenectomy for patients with advanced stage disease and utilize chemotherapy in the adjuvant setting. Black race was associated with increased mortality, though this risk was mitigated by increasing hospital volume. Advanced age, non-commercial insurance, increased medical comorbidity, and tumor grade were also associated with worse outcomes.

To date, this is the first study to demonstrate the effect of hospital volume on survival in endometrial cancer, and to adjust for this variable when considering disparate outcomes in minority women. However, a few points should be noted. First, early stage, low-risk endometrial

cancer, which accounted for two-thirds of the population in this paper, has a very good prognosis, and outcome events may come many years after diagnosis. The death recorded was not disease-specific, so the causes of death may be independent of cancer in a large majority of these patients. The authors do account for the patient's co-morbidity score at time of diagnosis, but in cases where these patients may go on to live much longer, that variable likely changes and may be of questionable validity. Second, it is important to keep in mind variations in treatment that occurred over the 13-year time period, and that temporal bias cannot be entirely excluded. Early in the 2000s, studies evaluating the need for lymph node dissection, including novel approaches to intraoperative decision-making, were evolving (14). There was also a growing interest in sentinel lymph node identification. And perhaps most importantly, minimally invasive surgery was growing in acceptance, and moving from traditional laparoscopy to robotics. The uptake of newer—and more expensive—technologies, such as robotics, was more likely to be at the larger centers. The potential range in surgical approaches, therefore, may not be comparable across the large study interval. Finally, as in all database studies, the reader lacks information which may significantly impact patient survival outcome, including reasons why a patient did, or did not, receive adjuvant chemotherapy and/or radiation. There are no data on patients who did not receive surgery at any time during their endometrial cancer care. Who are those patients? Is there a disparity in patients who present so late that they cannot undergo an attempt at hysterectomy? Additionally, while the authors investigate hospital-level data, they do not account for surgeon-level information. At an institution with more than 60 surgeries/year, does it matter if those surgeries are shared among 10 surgeons, who do just 6 cases each? Does the surgeon who works at a smaller hospital but who does 20 cases a year have better oncologic outcomes?

Perhaps the most striking finding in this study is that black women, who had worse survival, were more likely to be treated at high volume centers, where chemotherapy was more likely to be utilized and staging to be more aggressive. High-volume centers are more likely to be adherent to national treatment guidelines, and are more likely to have access to research protocols and novel therapeutics (7,15). One cannot help but wonder why black women, who are receiving care in centers of optimal delivery, still do more poorly than whites.

The answer is complicated, and multifactorial. An initial consideration may the differences in medical comorbidities between races. Black women are known to have higher rates of hypertension and vascular disease, and women with endometrial cancer are no different. Such comorbidities may ultimately affect survival, especially in low-grade endometrial cancers. But studies evaluating the influence of comorbidities and racial disparities in endometrial cancer survival have shown that even when accounting for chronic medical conditions, black women still do worse (16). Differences in care delivery between black women and white women have been observed, and are an important piece to the puzzle. Scalici *et al.* reported that there is a 10-fold lower expected participation by black women in Gynecologic Oncology Group (GOG) endometrial cancer clinical trials compared with whites, and that over the last several decades that number has steadily declined (17). In fact, black race was not reported on any GOG publication prior to 1994. Fewer black women also undergo minimally invasive surgery for endometrial cancer, even though laparoscopy mitigates disparities in immediate post-operative complications compared to white patients (18).

While epidemiologic studies are helpful to associate clinical factors with disparate outcomes, they fail to account for probably the most significant determinants of outcome—genetic risk factors and underlying tumor biology. Recently, The Cancer Genome Atlas (TCGA) demonstrated that there are four molecular subtypes of endometrial cancer: *POLE*-mutated hypermutated, microsatellite instability (MSI)-high, copy number low and copy number high. The copy number high subtype has the worse overall survival (19). Using data derived from the TCGA, investigators have compared the molecular features of endometrial cancers, and survival differences between black and white women (20,21). The most up-regulated gene in the tumors of black women was *Utf1* (undifferentiated embryonic cell transcription factor 1). This gene is directly controlled by *Oct4* and *Sox2*, pluripotency genes whose expression is associated with very aggressive undifferentiated tumors (22). The most frequently mutated gene in the endometrial tumors of black women was *TP53*, a tumor suppressor gene commonly aberrant in type II endometrial cancers. More intriguing is that among all patients with a *TP53* mutation, tumors from black women more frequently had increased somatic copy number variations (SCNV) associated with increased tumor aggressiveness. In fact, nearly two-thirds of tumors from black women were found to have a very high number of SCNVs (compared to only 23.5% of white women) associated with shorter progression free survival after treatment conclusion. Black patients also more frequently have tumors with amplifications

of chr1q. This region encodes for a family of S100A proteins, which are associated both with higher recurrence rates in breast cancer, as well as activation of the epithelial-to-mesenchymal phenotype which increases tumor metastasis (20). This correlates with the finding that black patients were more likely to have tumors with mitotically active subtypes, at a frequency twice that of white patients, and with a four-fold increased risk for shorter progression free survival (21). In contrast, white women were more likely to have tumors with mutations associated with hypermutated states and favorable prognoses, including *POLE* low copy number variations (20). These types of data can form the basis for the development of molecular targeted therapies to improve clinical outcome for specific subtypes of endometrial cancers which disproportionally affect black women.

While Buskwofie and colleagues make a strong argument that increasing hospital volume positively effects outcome, it is short-sighted to assign this single variable significant weight in the overall story of endometrial cancer in black women. The complex biology of the disease, along with the variations in surgical management, participation in clinical trials, and treatment of metastatic disease, none of which are captured by the NCDB, likely play larger roles in patient outcomes. Moving forward, understanding the mechanisms of mutagenesis, including hereditary predispositions, and advocating for novel screening techniques for women considered to be at the highest risk are crucial. Further elucidating the molecular mechanisms of tumorigenesis, and exploiting them as potential targets of novel therapeutics, will be vital. Modifying disparities in endometrial cancer outcome—beyond just race and ethnicity—will involve a number of approaches. But greater investment in patient education, and standardization of surgical management and adjuvant treatment, should continue to be priorities as we battle this disease.

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Footnote

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