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Conference Report: Symposium on Advances in Endometrial Cancer Epidemiology and Biology

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The NCI-supported symposium, “Advances in Endometrial Cancer Epidemiology and Biology,” brought together ∼70 investigators in epidemiology, biology, pathology, psychology, and clinical practice at the Harvard School of Public Health for two days in March 2014. Following presentations of recent work in seven topic areas, the concluding discussion identified research priorities for reducing the burden of this increasingly common cancer.

Endometrial Carcinogenesis

Douglas Levine, MD, presented data from The Cancer Genome Atlas (TCGA) to show that endometrial carcinomas display more diversity than captured by the current classification scheme (Type I and Type II) [1]. There were 4 broad groups identified: 1) an ultramutated group caused by mutations in the exonuclease domain of the POLE DNA polymerase; 2) a hypermutated group characterized by microsatellite instability and defects in mismatch repair factors; 3) a low copy-number group that exhibits microsatellite stability, and 4) a group characterized by chromosomal instability and high copy number variations. TCGA also identified several novel oncogenes and tumor suppressors. A subset of women with endometrioid type tumors who had amplifications in chromosome 1q had considerably worse outcomes. Approximately 25% of high-grade endometrioid tumors had extensive

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copy number alterations similar to high-grade serous tumors. The next step is to understand the key etiologic factors leading to the phenotypes identified. Marc Goodman, PhD, recommends collecting epidemiologic data from medical records for women whose tumors are included in TCGA and linking risk factors to tumor characteristics. The challenge is to obtain large numbers of well-annotated tumor specimens and epidemiologic data.

Paul Goodfellow, PhD, spoke on the mismatch repair pathway; although it has been studied for many years, the genes targeted by MMR defects in endometrial cancer remain elusive. Target genes differ from those in colorectal cancer: current candidates include JAK1, TFAM, PDS5B, and CTCF [2]. Whether these represent driver genes and are clinically relevant is not known. Ongoing work focuses on the genetic and environmental factors that contribute to somatic inactivation of mismatch repair; how these factors interact; whether MMR deficiencies can be prevented or the molecular evolution to cancer can be avoided; and what genes/pathways in MSI+ endometrial cancers are important for treatment.

Diego Castrillon, MD, PhD, has developed animal models to allow for study of endometrial cancer genes and pathways identified by TCGA. Animal models offer a rich potential resource for understanding the biology of endometrial carcinogenesis and meeting the goal of individualization of therapy, but have been underutilized. A mouse model generated to study inactivation of Lkb1 (an upstream regulator of the mTOR signaling pathway) revealed that this gene is a potent suppressor of endometrial cancer, and that Lkb1-driven tumors are sensitive to rapamycin therapy [3]. In clinical trials, mTOR inhibitors such as rapamycin have shown mixed results, but some responses have been shown in endometrial cancer. Mouse models also have promise for an improved understanding of how patterns of genomic instability (identified in TCGA) arise and result in specific histologic patterns and clinical behaviors. For example, a mouse model of endometrial cancer based on telomere instability combined with inactivation of p53 (Pot1a/p53 model) led to endometrial cancers with Type II features, whereas prior models resembled Type I tumors.

Pathology and etiologic heterogeneity

George Mutter, MD, discussed current findings and future directions in diagnostic categories of endometrial cancer. The common “Type I and Type II” terms are not accepted diagnostic terms [4]. Type II cancers have been inappropriately equated with serous cancers, although Type II includes other distinctive types such as clear cell carcinoma and carcinosarcoma. There are at minimum four different pathogenetic classes, each with its own clinical implications. Within the endometrioid category, the prognosis differs substantially according to grade: treatment failure is uncommon in grade 1 and 2 tumors, but rises to >40% in grade 3 tumors. For serous tumors, treatment failure is >60% [5]. The endometrioid pathway is characterized by inactivation of PTEN, changes in B-catenin and K-Ras, as well as microsatellite instability. Serous carcinomas are characterized by mutation in P53. Genetic profiles of clear cell carcinomas are poorly defined, and they may not be a homogenous type, [6] but preliminary reports indicate only a third are p53 mutant, with abnormalities of HNF-1 beta being more common [7]. The classification of endometrial carcinosarcomas was changed in 2002 by the WHO based on accumulated evidence that they are metaplastic carcinomas rather than sarcomas. Precursor lesions, endometrial intraepithelial neoplasia

(EIN), have been identified for endometrioid carcinomas. Less certain is whether serous intraepithelial carcinoma (serous EIC) is a bona fide precursor of serous cancers, as they contain most of the genetic changes of invasive lesions, and are capable of exfoliative metastasis in the absence of invasion. Therefore, they can be construed as the earliest stage of malignancy rather than a biologically distinctive precancer. Other factors influence disease course and outcome: myoinvasion, host response to myoinvasion, and lymphovascular invasion; potentially, hormonal responsiveness and sporadic or germline genetics will become useful in stratifying outcome or defining treatment groups.

Two epidemiologists addressed the question of risk factors in the less common, more lethal "Type II" tumors. Wendy Setiawan, PhD, presented work that was based on a pooled analysis of 24 studies from the Epidemiology of Endometrial Cancer Consortium (E2C2) [8], providing a large number of cases (>14,000) and controls (>35,000) with epidemiologic information on risk factors that allowed for study of 7 different subtypes, as well as the type I- type II classification. Overall, established risk factors influence both type I and type II cancers. Increasing body mass index (BMI) was significantly associated with risk for each type, although more strongly for the Type I tumors. Increasing parity was related to declining risk for all types except clear cell tumors. Ever using oral contraceptives and later age at last birth were equally protective for types I and II. Current smoking was strongly related to reduced risk in most subtypes. Overall, serous and mixed cell tumors appear to be less estrogen dependent and clear cell tumors appear to have a somewhat different risk profile.

Louise Brinton, PhD, examined the question of etiologic heterogeneity using a case-only analysis in a large GOG trial [9]. Compared to women with grade 1-2 endometrioid tumors, those with type II or endometrioid grade 3 tumors were less likely to be obese. They were more likely to have higher parity and to be current smokers, indicating that these factors had a less protective effect than for lower-grade endometrioid tumors. Use of tamoxifen for breast cancer was more common in women with type II tumors, while prior breast cancer without use of tamoxifen was more common in grade 3 endometrioid tumors. Other risk factors were generally similar for high grade endometrioid and type II tumors.

Genetic susceptibility and gene-environment interactions

David Hunter, ScD, provided an overview of studies of genetic susceptibility in cancer risk. The major contribution of these studies is providing additional insights into biology and disease mechanisms. Variants identified in GWAS can also be used to improve risk models, to select high-risk women for prevention trials, and to stratify women for screening. Most GWAS-associated variants have not shown interactions with lifestyle and environmental risk factors, suggesting that the variants represent biological processes independent of established risk factors.

Immaculata De Vivo, PhD, presented results of the 3 endometrial cancer GWAS to date. The first GWAS [10] reported one genome-wide significant association, at the 17q21 (*HNF1B)* locus, a locus associated with type 2 diabetes; this was confirmed in the two other GWAS [11, [12]. No additional loci have been identified, probably because of low statistical power.

An exome-wide association study of endometrial cancer did not identify rare variants [13]. Future plans are for a meta-analysis, gene-environment studies, and genetic susceptibility by molecular subtype.

Karen Lu, MD, described the 2 hereditary syndromes that have been identified in endometrial cancer: HNPCC (Lynch syndrome, involving germline mutations in one of 4 mismatch repair genes) and Cowden's syndrome (germline mutations in PTEN). For women with a mutation in these genes, the lifetime risk of uterine cancer is similar to colon cancer, about 40% to 60%. The 2-3% of women with endometrial cancer who have a Lynch syndrome mutation tend to be younger, have lower BMI, and have a first degree relative with a related cancer. Preventive measures, such as use of oral contraceptives or progesterone treatment, may be feasible in this population.

Risk prediction and early detection

Although the lifetime risk of endometrial cancer is relatively high, little work has been done to develop risk models. Ruth Pfeiffer, PhD, presented her work [14] on absolute risk, accounting for mortality from competing risks. A wide range of 20-year absolute risk was observed, from 1% to 15%. The discriminatory accuracy of the model (AUC=0.68) was adequate to use the model for risk stratification, although the investigators found that the model was not well calibrated. Jennifer Prescott, PhD, described a model that used more detailed information, including information on the timing of exposures, resulting in improved discriminatory ability. Future work involves validation in other cohorts, refining data on exposures, adding other risk factors, extending the models to African American women, and modeling by molecular subtype.

Diagnosis and treatment of endometrial hyperplasia (EH) offer an opportunity to prevent endometrial cancer, but little is known about natural history of hyperplasia. James Lacey, PhD, presented results of a study [15] in which women with a diagnosis of simple (SH), complex (CH), or atypical hyperplasia (AH) were studied retrospectively to determine the incidence of concurrent and subsequent cancer. In women with AH, 50% were found to have cancer at the time of hysterectomy and absolute risk of cancer over 20 years was 30%. Because a high proportion (80%) of AH patients undergo hysterectomy, the true burden of uterine cancer is higher than current rates indicate.

Women with high BMI, postmenopausal bleeding and hyperplasia are known to be at high risk, but there is no uniform management of these women. Methylation profiling of >800 cancer-related genes by Nico Wentzensen, MD, PhD, and colleagues has shown different patterns of methylation in endometrial cancer and normal tissue [16]. For 8 genes with significantly higher methylation levels in cases, an AUC of 0.91 was found; differences in all 8 were also replicated in TCGA samples. Sampling of the lower genital tract with Tao brushes and tampons showed that methylation markers for candidate genes were promising markers of risk. A prospective study is ongoing to further evaluate risk stratification based on methylation markers.

Racial disparities

Differences between black and white women in incidence and outcomes of endometrial cancer were summarized by Michele Cote, PhD. While incidence has been reported to be lower in black women, survival has been poorer for black women at every stage. When hysterectomy rates, which are higher in black women, are taken into account, incidence may actually higher in black women. Recent SEER data show increases in incidence in black women, for serous, clear cell, and endometrioid subtypes. Pooled data from E2C2 have shown that risk factors for endometrial cancer are similar in both racial groups [17]; although this is the largest study to date of risk factors in black women, data were still too sparse to evaluate some important variables. Even within GOG protocols with uniform eligibility requirements, outcomes are more favorable for white patients [18]. Larry Maxwell, MD, showed data demonstrating that differences in progression-free survival are strongly correlated with genetic admixture, with higher proportion of African ancestry related to poorer outcome. Black women are more likely to have serous, clear cell or undifferentiated tumors and more likely to have higher stage disease [19]. Molecular differences in tumors of black and white women include a chromosomal gain at 1q23 and expression of Her-2 Neu, while analyses of other tumor characteristics have not shown differences.

Alexandra Shields, PhD, advocated that research should integrate genetic, social, environmental, and behavioral levels of risk factors at every stage. GWAS studies have included very few African-Americans and physicians who serve minority populations are unlikely to recommend genetic testing [20]. Self-identified race does not necessarily correspond to geographical ancestry, and the degree of African ancestry in African Americans varies widely [21]. Very few studies have examined relationships between psychosocial factors and endometrial cancer [22, [23]. Incorporating measures of stress, the physical environment, and social environment requires cross-disciplinary collaboration.

Obesity and related mechanisms

Marc Gunter, PhD, discussed mechanisms that link obesity, diet and physical activity with risk of endometrial cancer. In the Women's Health Initiative, he and colleagues assessed baseline levels of markers of insulin resistance, adipokines, and inflammation in relation to risk, finding that estradiol and insulin were each associated with increased risk [24]. BMI does not completely correspond to metabolic health; these investigators found that normal weight women with metabolic risk factors were at increased risk. Dr. Gunter is also investigating the association of circulating markers of the insulin/IGF and sex hormone axes as well as tumor tissue gene and protein expression with tumor recurrence and mortality in high stage patients. In preliminary analyses, higher IGF-1 and IGFBP-3 levels are associated with lower risk of recurrence, while insulin is not.

The impact of intentional weight loss on markers of risk of endometrial cancer, including premalignant lesions, is being pursued by Faina Linkov, PhD, focused on pathways that could be influenced by weight loss. She and colleagues have found that intentional weight loss led to lower levels of systemic soluble e-selectin and IL-6 and increases in growth

hormone, adiponectin, and IFGBP-1. Weight loss induced by bariatric surgery influenced endometrial tissue markers such as CD20 and estrogen receptor [25]. Current work involves studying these variables in serum and endometrial tissue from women having bariatric surgery, at baseline and later time points. Early findings from baseline biopsies from women who are candidates for bariatric surgery suggest that 27% have subclinical endometrial pathology.

Ann Klopp, MD, PhD, studies the role of adipose derived stem cells (ASC) in endometrial cancer. Stromal cells from bone marrow and adipose tissue migrate to sites of tumors and form tumor stroma. Local fat tissue provides vascular and fibrovascular support for tumors and bone marrow derived cells that are recruited from the circulation promote cell motility and metastasis. A high waist-to-hip ratio, reflecting visceral adiposity, has been found to increase risk of endometrial cancer [26]. Visceral adipose tissue differs from peripheral adipose tissue: it is a common metastasis site for intra-abdominal cancers; it increases glucose-related markers; adipocytes are larger; it drains through the liver; there is more inflammatory cell infiltration; and accumulation is less influenced by estrogen. Dr. Klopp's studies have shown that obesity increased in-vivo tumor growth, ASC sphere formation and tumorisphere formation, and macrophage infiltration, while decreasing intra-tumoral adipocytes.

Shingo Kajimura, PhD, reported on his studies of brown and white fat. Brown adipose tissue differs from white adipose tissue: it dissipates energy; is found in multilocular droplets; has a high number of mitochondria; and is generally associated with less obesity. The goal is to change the fate of fat cells in order to burn more energy and fight obesity. Dr. Kajimura and colleagues are pursuing pharmacological approaches to induce development of brown/ beige fat [27, [28]. They used high-resolution phosphoproteome analysis to identify unique kinases in brown, beige, and white fat, identifying casein kinase II (CK2) as a negative regulator of beige fat development. The CK2 complex influences the cell cycle and cell survival, differentiation, and circadian rhythm. CK2 activity is induced in both subcutaneous and visceral white adipose tissue in obese mice fed a high-fat diet, while brown adipose tissue activity was not influenced by diet. CK2 is a promising pharmacological target for obesity and metabolic diseases, as well as for cancer.

Quality of life

Although there are more than 600,000 women in the US who are survivors of endometrial cancer, quality of life issues in this population have rarely been studied. Since 70% of endometrial cancer survivors are obese, work on quality of life has focused on the related issues of physical activity and diet. Dr. Basen-Engquist, PhD, reported that few endometrial cancer patients meet established guidelines for physical activity. Among those who do meet the guidelines, physical functioning is much higher, and pain and fatigue are less common [29], and physical activity interventions in cancer survivors have positive effects on health [30]. The “Steps to Health” study was a successful intervention using social cognitive theory to improve physical activity in endometrial cancer survivors [31]. Obese survivors realized similar benefits from exercise as nonobese survivors [32]. An intervention focused on diet as well as physical activity was reported on by Vivian von Gruenigen, MD, motivated by

reports that only 1% of endometrial cancer survivors meet 2006 ACS guidelines for cancer survivors [33]. In the randomized SUCCEED study, the intervention group showed improvements in physical activity, kilocalories consumed, and fruit and vegetable servings, as well as weight loss [34]. Self-efficacy was an important factor in achieving positive results. Currently, mobile technology is being used to encourage exercise and good nutrition, with regular contact being made with survivors of endometrial cancer [35].

Marcela del Carmen, MD, discussed survivorship issues after chemotherapy. Recent GOG studies identified toxicities associated with these drugs, including carboplatin, paclitaxel and doxorubicin. Late effects, including neuropathy, depression, pain, fatigue, and cognitive impairment, can be severe [36]. Prevalence of these late effects is likely to be higher in the future because of the increasing amount and complexity of treatment. There is little evidence of what constitutes best practices in caring for endometrial cancer survivors. Future research including longitudinal studies linking cancer treatment to late effects will help define optimal surveillance schedules for survivors.

Conclusions

Discussion by the attendees identified these priorities: 1) Collaborations between epidemiologists and pathologists should leverage TCGA results to more clearly define the tissue phenotypes and relate them to epidemiologic risk factors, treatments, and outcomes. 2) Future research on the striking disparities between black and white women should incorporate co-morbidities, access to care, and psychosocial factors, which have not been evaluated. 3) Risk models should be tested and refined to identify women at the highest risk who can be offered preventive measures and/or surveillance. 4) Biomarkers of etiologic pathways and risk have been identified and warrant continued study and eventual clinical use. 5) Studies of quality of life in survivors have shown promising results and should be expanded.

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