Gynecologic Oncology 130 (2013) 169–173

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Transcript expression in endometrial cancers from Black and White patients ☆

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HIGHLIGHTS

- The objective of this investigation was to determine whether gene expression among endometrial cancers is different between Blacks and Whites.
- Unsupervised analysis of the 50 endometrial cancers failed to identify global gene expression profiles unique to Black or White patients.
- These data revealed no gene expression differences and identified few individual gene differences between endometrial cancers from Blacks and Whites.

ARTICLE INFO

Article history:
Received 30 January 2013
Accepted 10 April 2013
Available online 17 April 2013

Keywords:
Endometrial cancer
Expression microarray
Racial disparity

ABSTRACT

Objective. Previous studies suggest that differences in molecular features of endometrial cancers between racial groups may contribute to the poorer survival in Blacks. The objective of this investigation was to determine whether gene expression among endometrial cancers is different between Blacks and Whites.

Methods. Fresh frozen tumors from 25 Black patients were matched by stage, grade, and histology to endometrial cancer specimens from 25 White patients. Each case was macrodissected to produce specimens possessing a minimum of 75% cancer cellularity. A subset of 10 matched pairs was also prepared using laser microdissection (LMD) to produce specimens possessing a minimum of 95% cancer cells. Total RNA isolated from each sample was analyzed using the Affymetrix Human Genome U133 Plus 2.0 arrays. Data were analyzed using principal component analysis and binary class comparison analyses.

Results. Unsupervised analysis of the 50 endometrial cancers failed to identify global gene expression profiles unique to Black or White patients. In a subset analysis of 10 matched pairs from Blacks and Whites prepared using LMD and macrodissection, unsupervised analysis did not reveal a unique gene expression profile associated with race in either set, but associations were identified that relate to sample preparation technique, histology and stage.

Conclusions. Our microarray data revealed no global gene expression differences and identified few individual gene differences between endometrial cancers from Blacks and Whites. More comprehensive methods of transcriptome analysis could uncover RNAs that may underpin the disparity of outcome or prevalence of endometrial cancers in Blacks and Whites.

Introduction

Racial disparity in endometrial cancer survival, particularly for Black patients, is significant [1,2]. In the United States, it is estimated that 4430 Black women would be newly diagnosed with endometrial cancer in 2011 with 1450 deaths, nearly twice what is seen in the general population (www.cancer.org). Black women appear to present with more aggressive disease, even when enrolled in healthcare systems with equal access to care [3]. Although the endometrial cancers diagnosed

☆ The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, Department of the Air Force, or the Department of Defense. This study was funded by the Department of Defense Peer Reviewed Medical Research Program, Award Number DAMD17-02-1-0183 and the United States Medical Acquisition Activity award W81XWH-11-2-0131.

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0090-8258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ygyno.2013.04.017

in Blacks are often non-endometrioid and poorly differentiated, survival is lower for Blacks in studies that control for stage, grade, histology, and surgical treatment [4]. In contrast, endometrial cancer is more prevalent in Whites and these cancers are usually endometrioid with more favorable prognosis. In aggregate, these clinical data support that the "aggressiveness" of endometrial tumors in Blacks may be attributable to specific molecular alterations characterizing a unique tumor biology [5].

Previous studies suggest a genetic and epigenetic etiology for the differences in observed tumor behavior among Blacks and Whites [6–9]. Mutations of the *TP53* tumor suppressor gene, which is associated with poor outcome, have been identified more frequently in Blacks than Whites with early stage (34% vs. 11%, respectively) [6] as well as advanced stage (55% vs. 25%, respectively) [7] endometrial cancers. In patients with advanced stage endometrial cancer, survival for Black patients was lower than in Whites, even after controlling for *TP53* mutation status, suggesting that other molecular alterations may contribute to this observed racial disparity for survival [7]. We subsequently analyzed other genes important in endometrial carcinogenesis and found that mutations in the *PTEN* tumor suppressor gene, which are associated with better survival, were more common in Whites than Blacks (22% vs. 5%, respectively) [8]. Other studies have suggested that differences in DNA methylation in endometrial cancers from Blacks and Whites might partially explain the racial disparity in outcome among patients with endometrial cancer [9]. Taken together, these studies that suggest the presence of unique molecular features in endometrial cancers from Black vs. White patients lend support to the racial disparity in outcome observed clinically.

Motivated by the above studies suggesting that molecular heterogeneity may contribute to racial disparities in outcome, we examined global patterns of gene expression in endometrial cancers from Blacks and Whites using RNA microarrays. Our previous investigations demonstrated global gene expression patterns differ by histology and grade [10–12]. The goal of this study was to determine whether patterns of gene expression differ between the Blacks and Whites when matched by grade, stage, and histology.

Methods

Tissue specimens

Flash frozen cancer specimens were obtained from 50 consenting patients undergoing surgery for uterine cancer at Duke University Medical Center and Memorial Sloan Kettering Cancer Center under IRB approved protocols. Specimens were harvested within 30 min of surgery and frozen until the time of the analysis. The set of endometrial cancers selected for this analysis included specimens from 25 Black and 25 White patients with racial status provided by the patients. The endometrial cancers from the two groups were matched by stage, grade and histology for the analysis.

All 50 specimens were evaluated by H&E to confirm and macrodissected to harvest at least 75% or greater cancer cells in each case. In a separate subset, 10 pairs of tumors from Black and White patients (matched by stage, grade and histology) were prepared using laser capture microdissection (LMD) (Subset 1). The same 10 pairs of tumors prepared using macrodissection were designated Subset 2.

Gene expression analysis

Cells procured by LMD from biospecimens in Subset 1 were collected in RLT Buffer plus 1% B-mercaptoethanol and total RNA was isolated directly using the RNeasy Micro Kit and quantitated with the Nanodrop 1000. Subset 2 samples were macrodissected directly from the frozen tissue specimen slides, where cancerous region collection was guided based on H&E stains from the same OCT tissue block. Total RNA was isolated using Trizol followed by an additional purification with the RNeasy Mini Kit. The integrity of each of the RNA samples was confirmed using Agilent Bioanalyzer RNA Pico or Nano Chips. In Subset 1, 100 ng of total RNA went through two rounds of amplification using the Affymetrix Two-Cycle cDNA Synthesis Kit. In Subset 2, 5 μg of total RNA went through one round of amplification using the Affymetrix One-Cycle cDNA Synthesis Kit. In both subsets, the Affymetrix Labeling Kit was used to produce biotinylated aRNA that was hybridized to Affymetrix HGU133A Plus 2.0 microarrays.

Gene expression was assessed using the Affymetrix (Affymetrix Inc., Santa Clara, CA) human genome U133 Plus 2.0 arrays (~54,600 probe sets). Approximately 5 μg of total RNA from each sample was labeled using the high yield transcript labeling kit (ENZO) and labeled RNAs were hybridized, washed and scanned according to the manufacturer's specifications (Affymetrix Inc., 2001). For macrodissected and LMD samples, Affymetrix one and two round amplification kits were used respectively. Expression Console (Affymetrix Inc.) software was used to determine signal values according to MAS5 algorithm. The signals on each array were normalized to a trimmed mean value of 500 excluding the lowest 2% and highest 2% of the signals. Statistical calculations were performed with Log_2 values of signals. An Affymetrix probe set representing a unique Gene Bank sequence is referred as transcript hereafter for convenience. The raw data has been deposited in GEO (XXX).

Data analysis

Unsupervised analysis was performed using multidimensional scaling (MDS) and principal component analysis (PCA). All transcripts on the array detected (MAS5 detection p-value < 0.0065) in at least in half of the samples were included for these analyses. Binary class comparison was performed on Blacks and Whites using Biometric Research Branch (BRB) Array tools software (BRB Array tools ver. 4.1.0, Richard Simon, Amy Peng, Biometric research branch, NCI, NIH, http://linus.nci.nih.gov/BRB-ArrayTools.html). Differentially expressed genes were identified by Analysis of variance (ANOVA) and paired T-tests. Analysis of variance was performed using a linear regression model.

Results

The histological characteristics of all 50 cancer specimens are shown in Table 1. Each of the 25 pairs of endometrial cancers from Black and White patients were matched by stage, grade, and histology. There were 10 early stage and 15 advanced stage cases per group. In the 50 specimens, there are 2 grade-1, 16 grade-2 and 32 grade-3 cases. In addition, 24 endometrioid cancers and 26 serous cases were evenly distributed between the Black and White women.

In the analysis of the 50 cases, one round of amplification was used to prepare RNA from macrodissected tissue specimens. Endometrial cancer cells from a subset of 10 matched pairs of endometrial cancer from Blacks and Whites were procured by LMD and in these cases two rounds of amplification were required to obtain sufficient RNA (Subset 1). To further evaluate the effects of sample preparation on the comparison of gene expression of endometrial cancer in Blacks versus Whites, we compared the expression data from the 20 cases prepared using LMD (Subset 1) to the same cases prepared by macrodissection (Subset 2). Median GAPDH 3'/5' ratios were 7.2 and 2.1 for Subset 1 and Subset 2, respectively, and median GAPDH signals were 17,805 and 31,400 for Subset 1 and Subset 2, respectively. Higher 3'/5' GAPDH ratios suggest differences introduced by the number of cycles of amplification. The scale factors were 7.4 and 11.9 for Subset 1 and Subset 2, respectively. Taken together, the distribution of expression levels clearly varies according to the amplification procedure utilized in sample preparation.

Global mRNA expression for the entire dataset of 50 samples of endometrial cancer was examined using PCA. This analysis enables the overall gene expression pattern of a sample to be expressed as a point in a three-dimensional figure and facilitates identification of clustering

Table 1
Pathologic features of endometrial cancers according to patient race.

Sample	Race	Histology	FIGO stage	Grade	Sample	Race	Histology	FIGO stage	Grade
1[a]	Black	E	IA	1	26[a]	White	E	IA	1
2[a]	Black	E	IA	2	27[a]	White	E	IA	2
3[a]	Black	E	IA	2	28[a]	White	E	IA	2
4	Black	E	IB	2	29	White	E	IB	2
5	Black	E	IC	2	30	White	E	IA	2
6[a]	Black	E	IC	2	31[a]	White	E	IC	2
7	Black	E	IC	2	32	White	E	IC	2
8	Black	E	IC	2	33	White	E	IC	2
9[a]	Black	E	IIB	3	34[a]	White	E	IIB	3
10[a]	Black	E	IIIA	2	35[a]	White	E	IIIA	2
11[a]	Black	E	IIIC	3	36[a]	White	E	IIIC	3
12	Black	E	IVB	3	37	White	E	IVB	3
13	Black	S	IB	3	38	White	S	IB	3
14	Black	S	IB	3	39	White	S	IB	3
15[a]	Black	S	IIIA	3	40	White	S	IIIA	3
16	Black	S	IIIC	3	41	White	S	IIIC	3
17	Black	S	IIIC	3	42	White	S	IIIC	3
18	Black	S	IIIC	3	43	White	S	IIIC	3
19	Black	S	IIIC	3	44	White	S	IIIC	3
20	Black	S	IVB	3	45	White	S	IVB	3
21	Black	S	IVB	3	46	White	S	IVB	3
22	Black	S	IVB	3	47	White	S	IVB	3
23[a]	Black	S	IVB	3	48[a]	White	S	IVB	3
24[a]	Black	S	IVB	3	49[a]	White	S	IVB	3
25	Black	S	IVB	3	50	White	S	IVB	3

[a] Samples selected for the analysis of Subset 1 and Subset 2.

of samples according to similar global gene expression profiles. The 25 matched pairs of endometrial cancers from Blacks and Whites revealed clustering of global gene expression by stage (Fig. 1A) and histology (Fig. 1B) but did not demonstrate sequestration by race (Fig. 1C). A subset PCA analysis of 10 matched pairs showed distinct clusters reflective of the method of preparation (i.e. Subset 1 and Subset 2) but the Black and White cases did not segregate from each other in either Subset (Fig. 2). The variances of the same data of 26,200 transcripts were also examined by principal component analysis (PCA). Unlike MDS that used correlation for comparison, PCA examines the data variance partitioned along principal components (PCs). The PCs are orthogonal to each other where the correlation among PCs is minimized. A projection on three principal components shown as a 3D graph in Fig. 2B indicates highest data variance by race (23% of total variance) along PC #1, although there is no clear segregation by race. The PC #2 explaining about 14% of the total variance shows distinctions between Subset 1 and Subset 2 similar to MDS analysis. Therefore, the technical variations are much more distinct than race differences in the present global expression profiles.

Expression data from the 50 cases of endometrial cancer was examined by ANOVA taking into consideration the stage, grade and histology of the tumor as well as the race of the patient. A summary of the numbers of transcripts identified by ANOVA at $p < 0.005$ for each race and the interaction terms between race and histology and between race and stage is given in Supplemental Tables 1–3. There were 303 transcripts altered by Race (Supplemental Table 1). This number does not represent a statistically significant global gene expression difference in a 54 K array since $\alpha = 0.005$ allows ~273 transcripts by random chance. The histologic type and stage dependent differences were found to be much higher (1964 and 1310 transcripts respectively) suggesting global differences, while race and grade have marginal significance. The differential expressions indicated by the interactions of race with histologic type (197 transcripts — Supplemental Table 2) and stage (268 transcripts — Supplemental Table 3) also do not represent significant global difference.

We also examined pair wise analysis by matching the clinical parameters between Black and White cases. Class comparison of gene expression in the 25 matched pairs of endometrial cancers from Blacks and Whites revealed that there are 273 transcripts at $p < 0.005$ in which 47 are altered by 2-fold (Supplemental Table 6). The global test p-value was 0.33 suggesting that there is no significant difference in gene expression between the endometrial cancer from Blacks and Whites. Similar analyses for the comparisons of histological types and stages I/II versus stages III/IV indicated global test p-values of 0.014 and 0.005 respectively.

Class comparison analysis between Black and White cases was done on Subset 1 data set separately using parametric paired T-tests (BRB Array Tools software Ver 4.1.0). This analysis identified 173 differentially regulated transcripts at $p < 0.005$. The probability of finding these 173 transcripts out of all 54,675 on the array by random chance was calculated as $p = 0.4$ confirming no significant global difference by race. Similarly, class comparison tests using Subset 2 data identified 224 differentially regulated transcripts between Blacks and Whites at $p < 0.005$ but the global p-value for the class comparison was $p = 0.3$. Class comparison analysis (using BRB Array Tools software) between Subset 1 and Subset 2 samples using two-sample T-tests identified 5264 transcripts at $p < 0.0001$ and indicated that the probability of finding this many transcripts by random chance is extremely small ($<1 \times 10^{-7}$). These data confirm that global gene expression differed by the technique used for sample preparation or the variation in resultant sample purity but did not differ between Blacks and Whites for either method (Subset 1 or Subset 2).

Discussion

Racial disparities in endometrial cancer outcome are multifactorial and may be related to inequalities in treatment, concurrent co-morbidities, or differences in the aggressiveness of the tumor. The Gynecologic Oncology Group (GOG) performed three ancillary studies assessing racial disparities in endometrial cancer outcome. All protocol patients received uniform treatment [13,14]. Black patients with advanced and recurrent endometrial cancer enrolled in multiple GOG trials had worse survival than White patients after controlling for age, performance status, stage, histology, tumor grade and treatment, stratified by protocol ($HR = 1.33$, $p = 0.0026$). In this analysis of 169 Black and 982 White patients, the overall response to adriamycin and platinum-based chemotherapy was 35% for Blacks and 43% for Whites ($p < 0.016$) suggesting that there may be the racial disparity in outcome

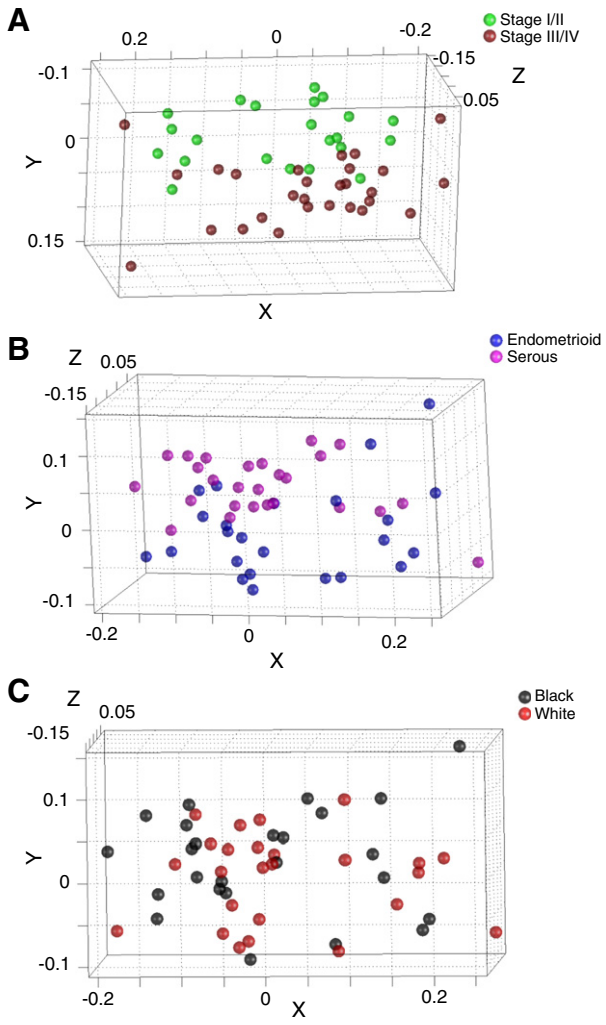

Fig. 1. Unsupervised analysis using multidimensional scaling (MDS) analysis based on the overall gene expression. A. stage I (green) and stage III/IV (maroon) B. Endometrioid (blue) and serous (pink); C. Black (black) and White (red).

which may in part be related to these cancers being less responsive to conventional therapy [11]. A subsequent study by the GOG on the same set of 1151 patients confirmed that the relative dose, relative time, relative dose intensity, and proportion of treatment related deaths or patients completing therapy were similar between Blacks and Whites, confirming a racial disparity in chemotherapeutic response [10]. To investigate the potential racial disparity in early stage endometrial cancer survival, the GOG also reported a retrospective analysis of 110 Black and 1049 White patients with stages I and II endometrial cancer on GOG 137. In this study, the relative risk of recurrence among Blacks receiving estrogen replacement therapy postoperatively was 11.2 (95% C.I., 2.86 − 43.59, $p = 0.0005$) when compared to Whites receiving similar treatment, even after controlling for confounding influences [12]. These three studies of endometrial cancer patients enrolled on clinical trials performed by the GOG suggested differences in tumor biology that in part explain racial differences in response to treatment outcome.

In order to globally assess differences in the molecular profile of endometrial cancers from Blacks and Whites, our group initially performed a preliminary comparison of gene expression using Affymetrix microarray. Fresh frozen tumors from 16 Black patients were compared to endometrial cancers from 24 White patients. Total RNA from each sample was analyzed using the Affymetrix HG133A and HG133B GeneChip set. In this preliminary study, there were 325 genes that were differentially expressed ($p < 0.005$) between the Black ($n = 14$) and White ($n = 24$) groups. The probability of this finding (at the $p < 0.005$ level) if there are no real differences was 0.045. Although we internally validated expression patterns of select transcripts using quantitative PCR, we had reservations about concluding that there were global differences in gene expression given the marginally significant results. We subsequently performed a global microarray comparison of 10 Blacks and 14 Whites in an independent sample set and did not find global differences in genes expression [13]. Of note, we did identify a transcript for phosphoserine phosphatase-like protein (PSPHL) that was overexpressed in both of our datasets [13] and the only other published microarray comparison of endometrial cancers in Blacks and Whites by Ferguson et al. [14]. However, the PSPHL transcript was increased in both the normal endometrial glands from Black patients without cancer as well as the endometrial cancers in Blacks [13] making this appear to be a race specific and not necessarily cancer specific biomarker.

Based on our contradictory data regarding global gene expression in endometrial cancers from Blacks and Whites [13], we acknowledged the limitations of our preliminary efforts and pursued a more definitive study. To strengthen the findings of this study, we first chose to use a more comprehensive microarray (U133 plus 2.0) and selected tissue specimens that allowed for paired comparison of cases matched for histology, grade and stage. Second, we used two methods of pre-analytical preparation and selected patients

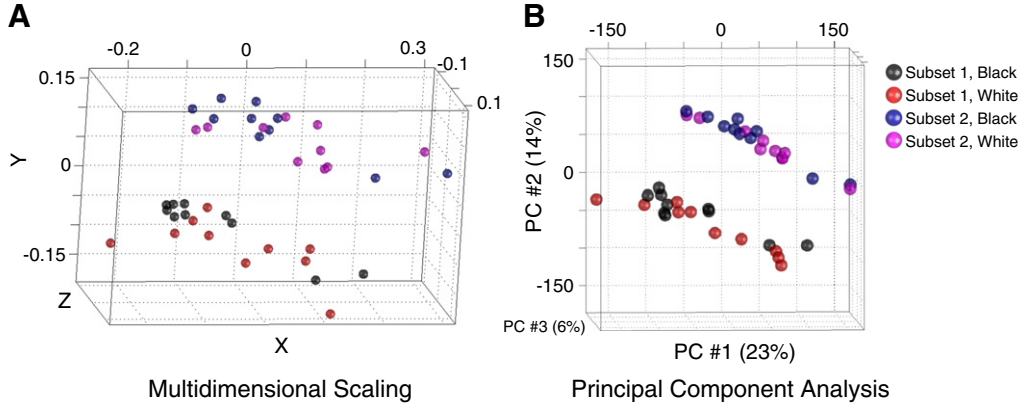

Fig. 2. Comparison of global expression profiles of 10 Blacks and 10 Whites (matched for histology, stage and grade) in Subset 1 and Subset 2. A. Multidimensional scaling using 1-correlation for distance measure. B. Projection of the principal components covering highest variance (43% of total variance). Note the segregation between Subset 1 and Subset 2 samples and lack of separation by race in both data sets. Note that Blacks are depicted as black and Whites are depicted as red in Subset 1 while Blacks are depicted as blue and Whites shown as pink in Subset 2.

with endometrial cancer from different areas of the country to provide more generalizable results. Third, we selected primarily stage I patients with endometrioid histology given that our group has previously reported a higher rate of recurrence among Blacks with early stage endometrial cancer receiving hormone replacement therapy [12]. Fourth we elected to comprise our sample set with a larger proportion of advanced stage cancers compared to early cancers since more profound effects of racial disparity in outcome for endometrial cancer patients are observed in those with stages III and IV of the disease [11,12]. Finally, the overall sample set was weighted to have equal distribution of serous and endometrioid tumors. Our analysis involved 100 microarrays of endometrial cancers from Blacks and Whites.

The only other published study that has compared gene expression in endometrial cancers from Blacks and Whites was performed by Ferguson et al. [14] wherein tumors from 14 Black and 25 White women were analyzed and 16 genes were noted to be differentially expressed at $p < 0.001$. This finding was not statistically different from that expected by chance alone [14]. Limitations in the study design by Ferguson et al. [14] prevented a definitive conclusion for which our current study more effectively provides. In our study, equally weighted groups of Blacks and Whites with endometrial cancer that were matched by histology, grade, and stage were utilized to avoid mixed class comparison procedures or two-sample T-tests that would be less than ideal in the analysis of small numbers of tumors from Blacks and Whites. Despite the improvements in study design and analysis, we demonstrated that there are limited gene expression differences using Affymetrix microarray between Blacks and Whites.

Our study also confirmed that differential gene expression appears to be primarily associated with stage and histology (Fig. 1) and future studies of racial disparities will need to control for these variables that can be more often found among Blacks thereby introducing bias. In addition, our study also highlights the importance of how pre-analytical preparation and amplification techniques can influence overall gene expression differences.

Similar studies comparing either breast or prostate cancer from Blacks and Whites have yielded similar results and similar recurring gene transcripts [15–17]. For example a comparison of Blacks and Whites with prostate cancer revealed the differential expression of statistically significant transcripts some of which were also identified in the comparisons we performed (i.e. PSPHL, SOS1, LTF and CRYBB2) [15–17]. Previous in vitro studies have confirmed the functional relevance of upregulated SOS1 in Blacks with prostate cancer [16] and our study also identified a single probe set of SOS1 upregulated in Blacks with endometrial cancers. The functional relevance in Black endometrial cancers remains to be investigated but the known function of up-regulated SOS1 is consistent with pro-oncogenic phenotypes.

The growing body of literature that have failed to identify gene expression differences in tumors from Blacks and Whites should not temper the pursuit of biologic etiologies associated with racial disparities in endometrial cancer outcome. Newer methods of gene sequencing facilitate much more comprehensive analysis of the transcriptome than hybridization-based microarray methodologies can provide, allowing for detection of low-expressed genes, alternative splice variants, and novel transcripts [18]. In addition, inclusion of miRNA and lncRNA data, provided through whole transcriptome deep sequencing (RNA-seq), may facilitate assessment of the competing endogenous RNA (ceRNA) activity which has been proposed as a regulatory network of coding (mRNA) and non-coding (miRNA, lncRNA) elements within the transcriptome [19]. An improved understanding of this network may help explain inconsistencies often noted between gene and protein expression and further support efforts to understand racial disparities in cancer outcome.

Racial disparities in endometrial cancer survival likely reflect a complex interaction between environmental exposures and genetic or epigenetic effects that differ between races. There is a clear need to integrate all these factors and to extend these findings into underlying biologic differences. Building on past work, additional studies using the latest technologies and workflows are needed to delineate the relative contributions and interactions between these factors in development and progression of endometrial cancers in Black women. Hopefully, a better understanding of the basis for racial differences in endometrial cancer will facilitate the development of prevention and treatment strategies that address the present disparity in outcome.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2013.04.017.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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