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TITLE: Significance of Pathways Leading to RhoC Overexpression in Breast Cancer

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| 13. SUPPLEMENTARY NOTES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |             |                                  |                            |                                                           |                                           |
| 14. ABSTRACT<br>Tumor biology is a recognized determinant of tumor behavior, including growth rate, motility and metastatic potential, and therapeutic resistance. This project was funded to investigate the regulation and expression of an excellent marker for aggressive breast tumors: RhoC-GTPase. When overactive, RhoC transforms mammary epithelial cells into a highly motile and invasive phenotype. We hypothesize that RhoC overexpression may be regulated by the transcription factor NF-kappa B and that at the same time RhoC is overexpressed the tumor also acquires therapy resistance. The objective of this study is to utilize existing breast cancer cohorts with tumor tissue and treatment response data available to assess the correlation between NF-kappa B and RhoC, individually and in combination, to treatment response. The specific aims of the project are to determine 1) if RhoC and NF-kappa B are correlated; 2) if RhoC and NF-kappa B are associated, individually and in combination, with aggressive breast cancer; and 3) if NF-kappa B and RhoC are associated with therapy resistance. |             |                                  |                            |                                                           |                                           |
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## INTRODUCTION

This study was funded to assess the relationship of RhoC and NF-kappa B to aggressive, metastatic, and therapy-resistant breast cancer. Inflammation is currently being considered a key component of cancer initiation and progression. [1] Many proinflammatory stimuli act through an NF-kappa B dependent signaling pathway. It is likely that RhoC, which is recognized as an important marker of breast cancer, aggressiveness is also regulated by NF-kappa B.

The tumor microenvironment is exceptionally critical in our understanding of cancer development. Recent research suggests that chronic inflammation is triggered during tumor growth. The tumor associated inflammation contributes greatly to the tumor microenvironment and perhaps even to tumor macroenvironment. Tumor-associated macrophages (TAMs) secrete numerous signaling molecules that interact with tumor and stromal cells. Secretion of TNF- $\alpha$  by TAMs activates NF-kappa B within the tumor cell through the receptor tyrosine kinase pathway.

Rho-GTPases are members of the Ras-superfamily. Activation of Rho promotes both the bundling of actin filaments with myosin II filaments into stress fibers and the clustering of integrins and associated proteins to form focal contacts. [2] Experiments conducted within the Merajver laboratory have shown an active role for RhoC in rearrangement of the cytoskeleton in cell motility and invasion.

We hypothesize that NF-kappa B is a transcription factor for the RhoC gene and leads to overexpression of cellular RhoC protein. As more is learned about these tumor markers, the potential exists for improved clinical diagnosis, prognosis, and treatment. The purpose of the study is to understand the regulation of RhoC gene expression in an epidemiological setting. A clear understanding of the genetic and cellular mechanisms involved in modulating a highly metastatic phenotype is expected to aid in diagnosis and treatment.

The scope of this work includes the identification and collection of patient information from Henry Ford Health system (HFHS). HFHS is an integrated health system that offers a diverse, population-based patient population from which strong epidemiologic studies can be built. Patient information, including diagnostic and recurrence data, will be combined with gene expression data. Molecular and statistical analysis will occur in collaboration with the University of Michigan.

## BODY

We are currently working in a no-cost extension. We are working to finish the last task of the project. Below are the objectives from the original statement of work.

- Task 4.* Prepare manuscript
- a. Complete final data analyses and tables
  - b. Prepare draft manuscripts
  - c. Mentor and collaborators review of draft manuscripts
  - d. Prepare final manuscripts and submit for publication

The analytic dataset for this project has been built. We have also updated the follow-up and outcomes data for the cohort, which was originally collected in 2005, so that the most current data is available for the final analysis. We have built 5 tumor microarrays (TMAs). Ms. Alford and Dr. Kleer have been working together to score the stained TMAs. We have completed the staining and scoring of RhoC and the staining of NFkB. The NFkB scoring will be complete by the end of June. Once the NFkB scoring is complete then the final analysis for the main aims of the study will be finished. We expect that the analysis and manuscript development and submission will be completed by the end of 2008. Ms. Alford is planning is expect to graduate in December 2008.

We have also begun to use the TMAs to investigate other genes. Working with Dr. Kleer, we scored the initial TMA for EZH2 (Polycomb group protein Enhancer of zeste-2) and found a significant relationship with estrogen and progesterone negative tumors. These tumors are resistant to hormonal manipulation which limits clinical treatment options for these patients. Since many of our cases were identified before Her2-neu testing was standard practice, we have also stained and scored all the TMAs for Her2-neu expression so that future analyses could also evaluate triple negative tumors (i.e., tumors that are negative for estrogen, progesterone, and Her2-neu). Using the preliminary EZH2 data, Ms. Alford submitted an abstract entitled "Epidemiology of the Polycomb group protein Enhancer of zeste-2 (EZH2) in aggressive early stage breast cancer". This abstracted was accepted for a poster presentation at the joint Metastasis Research Society-American Association of Cancer Research meeting in August. It represents work done in collaboration with Drs. Merajver, Gruber, and Kleer. **This work is being prepared for a manuscript.**

Other research activities, supported in part by funding from this grant, have included working with a multi-institutional collaboration between Henry Ford Health System, University of Michigan, Wayne State University, and Oakwood Hospitals. This collaboration is focused on cancer epidemiology research within the significant Arab American population in metro-Detroit. Arab women have been reported to have an increased incidence of inflammatory breast cancer (IBC), a particularly aggressive form of breast cancer. RhoC has been shown to be amplified in inflammatory breast cancer and may likely be the key to IBC's aggressive phenotype. [1] We recently published this research in Breast Cancer Research and Treatment. [2]

**Ms. Alford is also working on a manuscript focused on the influence of non-steriodal anti-inflammatory drugs on recurrence of colorectal cancer. Recently, Ms. Alford also published a Nature Reviews article with her collaborators from the Multiplex Initiative.**

**This study is investigating the uptake and personal utility of multiplex genetic testing for common chronic diseases, including cancer. Finally, Ms. Alford started teaching this fall a cancer biology course for a community nursing program.**

#### KEY RESEARCH ACCOMPLISHMENTS

- Updating and finalizing all the medical record information
- Identification of the appropriate tumor blocks for each case and building the tumor microarrays
- Staining and scoring the TMAs for RhoC and Hers-neu expression

#### REPORTABLE OUTCOMES

Reportable outcomes are expected for the next review.

#### CONCLUSIONS

Exciting research has surfaced in the past year regarding the tumor microenvironment and breast cancer metastasis. Areas which our genes of interest are likely to play a significant role. Despite this, no one else is currently investigating our genes of interest and their role in an aggressive breast cancer phenotype. As clinical oncology looks more to targeted therapy for treatment options, our work will hopefully be able to provide valuable insight for drug development.

#### REFERENCES

- [1] van Golen KL, Davies S, Wu ZF et al. A novel putative low-affinity insulin-like growth factor-binding protein, LIBC (lost in inflammatory breast cancer) and RhoC GTPase correlate with the inflammatory breast cancer phenotype. Clin Cancer Res 1999;5:2511-9.
- [2] Hensley Alford S, Schwartz K, Soliman A, Johnson CC, Gruber SB, Merajver SD. Breast cancer characteristics at diagnosis and survival among Arab-American women compared to European- and African-American women. Breast Cancer Research and Treatment 2008; April 15 [Epub ahead of print].

September 2008

CURRICULUM VITAE

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EDUCATION

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Bachelor of Science (Health Education)

1999 University of Michigan, Ann Arbor, MI  
Masters of Public Health (Epidemiology)

2008 (expected) University of Michigan, Ann Arbor, MI  
Doctor of Philosophy in Epidemiology

PROFESSIONAL EXPERIENCE

1992 Program Coordinator, American Diabetes  
Association, NW Ohio, Toledo, OH

1993-1995 Rural Community Education Volunteer,  
U.S. Peace Corps, Solomon Islands, South  
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1996-1997 Secretary, Industrial and Operations  
Engineering, University of Michigan, Ann  
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1997-1998 Research Assistant, Department of  
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2000- Epidemiologist, Henry Ford Health System,  
Detroit, MI

2008- Adjunct faculty, Henry Ford Community  
College

#### TRAINEESHIPS

|           |                                                         |
|-----------|---------------------------------------------------------|
| 1998      | US Public Health Traineeship (JRCOSTEP)                 |
| 2003-2008 | Department of Defense Pre-doctoral<br>Traineeship Award |

#### MEMBERSHIPS IN PROFESSIONAL SOCIETIES

|       |                                          |
|-------|------------------------------------------|
| 1992- | Society of Epidemiologic Research        |
| 1993- | American Society of Human Genetics       |
| 2000- | American Association for Cancer Research |
| 2008- | Metastasis Research Society              |

#### HONORS AND AWARDS

|         |                                                               |
|---------|---------------------------------------------------------------|
| 1990    | Delta Psi Kappa Honorary<br>Golden Key National Honor Society |
| 1991    | Distinguished Service Award, Miami<br>University              |
| 1991-92 | Miami University, Scholar-Leader                              |
| 1992    | Miami University, Cum Laude                                   |
| 2000    | Distinguished Alumni Award, Miami<br>University               |

#### TEACHING ACTIVITIES

|      |                                                                                                                                            |
|------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 2001 | Co-Teacher<br>University of Michigan Graduate Summer<br>Session in Epidemiology<br><i>Pediatric Asthma &amp; Allergy</i>                   |
| 2008 | Professor<br>AH135 3 credits<br>Henry Ford Community College<br>Health Careers Division<br><i>Fundamentals of Cancer &amp; Cancer Care</i> |

#### COMMITTEE AND ADMINISTRATIVE SERVICE

|       |                                                                                                                 |
|-------|-----------------------------------------------------------------------------------------------------------------|
| 2005- | Department of Biostatistics and Research<br>Epidemiology<br><i>CEPC Grand Rounds Working Group</i>              |
| 2006- | Michigan Department of Community Health<br><i>Newborn Screening Dried Blood Spots<br/>BioBank Working Group</i> |
| 2006- | Center for Organ Failure Solutions<br><i>Advisory Member</i>                                                    |
| 2007- | Karmanos Cancer Center<br><i>Cancer in Arab Americans Working Group</i>                                         |



## PEER-REVIEWED PUBLICATIONS

### Pharmacoepidemiology

Ulcickas Yood M, Quesenberry CP, **Hensley Alford S**, Tsai A, Wells KI, Yood MU, Ackermann SM, Shiff SP. An observational study examining the impact of capecitabine on warfarin antithrombotic activity and bleeding complications. *Current Medical Research and Opinion* 2006;22(2):307-314.

**Hensley Alford S**, Yood MU, Jankowski M, Rolnick S, Johnson CC. Non-steroidal anti-inflammatory drugs and colorectal cancer recurrence. Submitted.

**Hensley Alford S**, Gruber SB, Merajver SM. Effect of bisphosphonate exposure on incident breast cancer. Submitted.

### Asthma-Allergy Epidemiology

Johnson CC, Ownby DR, **Hensley Alford S**, Havstad S, Williams LK, Zoratti EM, Peterson EL, Joseph CLM. Antibiotic exposure in early infancy and risk for childhood atopy and asthma. *Journal of Allergy and Clinical Immunology* 2005;115(6):1218-24.

**Hensley Alford S**. Reply to comments on “Parental History of Atopic Disease: Disease pattern and risk of pediatric atopy in offspring.” *Journal of Allergy and Clinical Immunology* 2005;116(1): 232. DOI: 10.1016/j.jaci.2005.03.009

**Hensley Alford S**, Johnson CC, Peterson EL, Ownby DR, Zoratti E. Parental History of Atopic Disease: Disease pattern and risk of pediatric atopy in offspring. *Journal of Allergy and Clinical Immunology* 2004;114:1046-50. An Editor’s Choice article for that issue.

Johnson CC, Ownby DR, Zoratti EM, **Hensley Alford S**, Williams LK, Joseph CLM. Environmental Epidemiology of Pediatric Asthma and Allergy. *Epidemiologic Reviews* 2002;24:154-175.

Johnson CC, **Hensley Alford S**. Do animals on the farm and in the home reduce the risk of pediatric atopy? *Current Opinion in Allergy and Clinical Immunology* 2002;2(2):133-9.

### Molecular & Genetic Epidemiology

McBride C, **Hensley Alford S**, Reid R, Larson E, Brody L. Putting science over supposition in the arena of personalized genomics. *Nature Genetics* 2008;40(8):939-42.

**Hensley Alford S**, Schwartz K, Soliman A, Johnson CC, Gruber SB, Merajver SD. Breast cancer characteristics at diagnosis and survival among Arab-American women compared to European- and African-American women. *Breast Cancer Research and Treatment* 2008; April 15 [Epub ahead of print].

Lo AC, Kleer CG, Banerjee M, Omar S, Khaled H, Eissa S, Hablas A, Douglas JA, **Hensley Alford S**, Merajver SD, Soliman AS. Molecular epidemiologic features of inflammatory breast cancer: a comparison between Egyptian and US patients. *Breast Cancer Research and Treatment* 2007; Dec. 4 [Epub ahead of print].

Ford ME, **Hensley Alford S**, Britton D, McClary B, Gordon HS. Factors influencing perceptions of breast cancer genetic counseling among women in an urban health care system. *Journal of Genetic Counseling* 2007;16(6):735-53.

**Hensley Alford S**, Mouchawar J. Letter to the Editor regarding “Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer” Armstrong K, et al. *JAMA* 2005;295:677.

Mouchawar J, Laurion S, Ritzwoller DP, Ellis J, Kulchak-Rahm A, **Hensley Alford, S**. Assessing Controversial Direct-To-Consumer Advertising for Hereditary Breast Cancer Testing: Reactions from Women and their Physicians, and Costs to a Managed Care Organization. *American Journal of Managed Care*. 2005;11:601-608.

Rolnick S, **Hensley Alford S**, Kucera G, Fortman K, Jankowski M, Butani A, Ulcickas Yood M, Johnson CC. Racial and Age Differences in Colon Examination Surveillance Following a Diagnosis of Colorectal Cancer. *Journal of the National Cancer Institute Monograph* 2005;35:96-101.

Mouchawar J, **Hensley Alford S**, Laurion S, Finucane M, Meenan R, Ellis J, Rahm A, Pollack R, Ritzwoller D. Genetic Counseling Referral and Testing Impact of Direct-to-Consumer Advertising for Hereditary Breast Cancer Testing at a Managed Care Organization: A Naturally-Occurring Experiment. *Genetics in Medicine* 2005;7(3):191-197.

Mouchawar J, Goins KV, Somkin C, Puleo E, **Hensley Alford S**, Geiger AM, Taplin S, Gilbert J, Weinmann S, Zapka J. Guidelines for breast and ovarian cancer genetic counseling referral: adoption and implementation in HMOs. *Genetics in Medicine* 2003;5(6):444-450.

#### Epidemiology Methods

**Hensley Alford S**, Lappin R, Peterson E, Johnson CC. Pregnancy Associated Smoking Behavior and Six Year Recall. *Journal of Maternal and Child Health* 2008 (in press)

Thwinn SS, Clough-Gorr KM, McCarty MC, Lash TL, **Hensley Alford S**, Buist DSM, Enger SM, Field TS, Frost F, Wei F, Silliman RA.

## PRESENTATIONS

Shaping the future of personalized genomic information—Today. American Society of Human Genetics, Annual Meeting 2008.

Breast cancer characteristics at diagnosis among Arab-American women compared to European- and African-American women in the Detroit SEER registry. National Arab American Medical Association, Annual Meeting 2006.

## SELECTED POSTERS (from 25)

**Hensley Alford S**, Merajver SD, Gruber SB, Gad HO, Kleer “Epidemiology of the Polycomb group protein Enhancer of zeste-2 (EZH2) in aggressive early stage breast cancer.” Joint Metastasis Research Society-American Association for Cancer Research Meeting, Vancouver, British Columbia, 2008.

Nathanson SD, Kapke A, **Hensley Alford S**. “Sentinel Lymph Node Positivity and Future Metastases.” Society of Surgical Oncology Annual Meeting, 2008.

Lo A, Soliman AS, Kleer CG, **Hensley Alford S**, Eissa SS, Hablas A, Khaled HM, Omar S, Merajver SD. “Molecular epidemiologic features of inflammatory breast cancer: a comparison between Egyptian and US patients.” American Association for Cancer Research Annual Meeting, Los Angeles, CA, 2007.

**Hensley Alford S**, Schwartz K, Soliman A, Gruber S, Douglas JA, Johnson CC, Merajver SD. “Breast cancer characteristics at diagnosis among Arab-American women compared to European- and African-American women in the Detroit SEER registry.” San Antonio Breast Cancer Symposium, 2005.

## RESEARCH SUPPORT

### Recently Awarded:

(number pending) Hornbrook (PI), Hensley Alford (Site PI) 8/1/2008-4/30/2010  
NCI  
Building a Pharmacovigilance Population-Based Laboratory

This study is designed to develop systematic ways of identifying breast cancer recurrence in automated data sources of several health maintenance organizations involved in the Cancer Research Network. In addition, adverse events to anthracyclines will also be assessed.

(number pending) Silliman (PI), Hensley Alford (Site PI) 9/1/2008-8/31/2009  
NCI  
Breast Cancer Surveillance in a Defined Population: Automated Recurrence Supplement

This study is a supplement to the Breast Cancer Treatment Effectiveness in Older Women study. The supplement expands the data collection of the original cohort to include breast cancer recurrence and cost-benefit analysis.

Ongoing:

U19 CA79689 Larson (PI), Hensley Alford (Site PI) 3/1/2007-2/28/2009  
NIH/NCI & NHGRI  
Decisions of Young Adults Regarding Multiplex Genetic Testing for Common Disease

The goal of this project is to assess the information seeking and decision-making behaviors of young adults regarding testing for genetic variations that confer small increases in risk for common diseases.

W81XWH-04-1-0395 Hensley Alford (PI) 3/24/2004-3/23/2008  
DoD Pre-doctoral Trainingship Award

Significance of Pathways Leading to RhoC Overexpression in Breast Cancer

In a population based sample of breast tumors, the goal of this project is to compare the relationship of RhoC and NF-kappa B expression to aggressive tumors while controlling for demographics and treatment.

# Breast cancer characteristics at diagnosis and survival among Arab–American women compared to European– and African–American women

Sharon Hensley Alford · Kendra Schwartz ·  
Amr Soliman · Christine Cole Johnson ·  
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**Abstract** *Background* Data from Arab world studies suggest that Arab women may experience a more aggressive breast cancer phenotype. To investigate this finding, we focused on one of the largest settlements of Arabs and Iraqi Christians (Chaldeans) in the US, metropolitan Detroit— a SEER reporting site since 1973. *Materials and methods* We identified a cohort of primary breast cancer cases diagnosed 1973–2003. Using a validated name algorithm, women were identified as being of Arab/Chaldean descent if they had an Arab last or maiden name. We compared characteristics at diagnosis (age, grade, histology, SEER stage, and marker status) and overall survival between Arab–, European–, and African–Americans. *Results* The cohort included 1,652 (2%) women of Arab descent, 13,855 (18%) African–American women, and

63,615 (80%) European–American women. There were statistically significant differences between the racial groups for all characteristics at diagnosis. Survival analyses overall and for each SEER stage showed that Arab–American women had the best survival, followed by European–American women. African–American women had the poorest overall survival and were 1.37 (95% confidence interval: 1.23–1.52) times more likely to be diagnosed with an aggressive tumor (adjusting for age, grade, marker status, and year of diagnosis). *Conclusion* Overall, Arab–American women have a distribution of breast cancer histology similar to European–American women. In contrast, the stage, age, and hormone receptor status at diagnosis among Arab–Americans was more similar to African–American women. However, Arab–American women have a better overall survival than even European–American women.

Stephen B. Gruber and Sofia D. Merajver contributed equally to this work.

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**Keywords** Arab · Breast cancer · Epidemiology ·  
Incidence · Survival

## Background

Several papers from major treating hospitals in Arab countries have reported an early age of onset and a preponderance of aggressive breast cancer phenotype in their patients [1–12]. For example, papers from Tunisia report observations of rapidly progressing breast cancer in young women, suggestive of an inflammatory breast cancer (IBC) histology [5–8]. In addition, others have reported that the majority (>50%) of breast cancer cases are diagnosed among women less than 50 years of age [1, 3, 9]; this is in comparison to US statistics which show that 22% of breast cancer cases are diagnosed in women under 50.

While these statistics give some relative comparisons, they are difficult to interpret given the variation in the population age structure between Arab countries and the US, and the lack of detailed comparative studies between the US and Arab populations. In addition, it cannot be assumed that all breast cancer cases are systematically captured in most Arab countries, given the extreme paucity of systematic population screening for early detection in those regions. The well-established tumor registry in Israel gives data for the Jewish and Arab populations separately. Age-adjusted and standardized incidence rates from this registry show that the Israeli Arab population has a lower overall incidence of breast cancer compared to the US (36.7 per 100,000 compared to 97.2 per 100,000) and a later age at onset. Recently the Middle East Cancer Consortium (MECC), in conjunction with the US National Cancer Institute (NCI), published cancer statistics from four Middle East countries: Israel, Cyprus, Jordan, and Egypt (Tanta) [13]. The Tanta registry in Egypt, which is also population based, reports age-adjusted and standardized incidence rates of breast cancer higher than those of the Israeli Arab population for women <60 years as well as a higher overall incidence rate of 50 per 100,000. It is possible that given the diversity of the populations of the Arab world, the breast cancer experience varies among groups. Such variation, if it does exist, could be due to differences in genetic background, environmental exposures, or reproductive behaviors.

Metropolitan Detroit is home to the largest Arabic-speaking population outside of the Middle East. The city of Dearborn, the near west suburb of Detroit, has been a center of Arab culture and immigration since the late 1800s. Immigrant populations include Yemenis, Syrians, Palestinians, Egyptians, and Iraqis, including Chaldeans (Christian Iraqis). Political unrest in other Arab countries has also contributed to the heterogeneity of the Detroit Arab population. According to the 2000 Census, which included the option to report country of origin, the metropolitan Detroit Arab population is 44% Lebanese, 32% Chaldean, 10% Iraqi, 6% Syrian, 3% Palestinian, 2% Egyptian, and 2% Jordanian [14]. This Census data was collected before 9/11/2001, when fear of discrimination among American Arab and Muslim populations increased dramatically; therefore, the reported proportions are thought to be representative, despite the usual expected undercount from self-reported statistics.

Detroit has been part of the NCI's national tumor registry, the Surveillance Epidemiology and End Results (SEER) program, since the registry's inception in 1973. The large Arab-American community in Detroit gave us the opportunity to characterize in a population-based framework, the patterns of breast cancer experienced by Arab women versus other ethnic groups. Our work was highly facilitated by the advent of a validated name algorithm, which allowed the identification of women of Arab descent in the registry so

that a comparison could be made to white, non-Hispanic (European) and African-American women [15]. Our *a priori* hypothesis, based on the papers from the Arab world, was that Arab-American women would have poorer prognostic characteristics at the time of diagnosis than European-American women and worse survival.

## Methods

In contrast to the behavior of many other migrating populations, Arabs have maintained their cultural names after immigrating and settling in the US. Using a previously published and validated algorithm to identify Arab ethnicity by name [13], we identified women with an Arab last or maiden name in the Detroit SEER registry. We used data from the start of the registry in 1973, up to and including 2003. We compared women identified as being Arab to non-Hispanic, non-Arab Caucasian women (henceforth termed European-American) and to African-American women. The small percentage of women with other racial identities were excluded from this analysis.

We compared Arab women to European- and African-American women on several prognostic indicators at diagnosis including age, histology, grade, estrogen (ER) and progesterone (PR) marker status, and SEER stage. For each indicator, we first tested for global association with race using a  $\chi^2$  test. For indicators with a significant  $\chi^2$ , we calculated the odds ratio (OR) for that factor by race to characterize the variation.

We evaluated overall survival using Kaplan-Meier and Cox Proportional Hazard models for each racial group. Adjusted hazard ratios were calculated for each race adjusting for age, grade, ER/PR marker status, SEER stage, histology and year of diagnosis. We tested for interactions between race as well as age and each of the prognostic characteristics; significant interactions were retained in the model along with their main effects.

## Results

### Study cohort

There were 80,316 women diagnosed with primary breast cancer in the Detroit SEER registry between 1973 and 2003. We excluded 9 females diagnosed <18 years of age, 1,095 women with a race/ethnicity other than Arab-, European- or African-American, and 91 cases were excluded due to uncommon non-mammary epithelial histology (e.g., melanoma of the breast). The resulting analytic sample ( $n = 79,121$ ) was 80% European-American, 18% African-American, and 2% Arab-American. (Table 1) The overall

**Table 1** Study population characteristics

|                       | <i>n</i> (%) |
|-----------------------|--------------|
| Race                  |              |
| Eur <sup>a</sup>      | 63,614 (80%) |
| Afr                   | 13,855 (18%) |
| Arb                   | 1,652 (2%)   |
| SEER stage            |              |
| In situ               | 9,643 (12%)  |
| Local                 | 36,622 (46%) |
| Regional              | 23,754 (30%) |
| Distant               | 4,652 (6%)   |
| Unknown               | 4,450 (6%)   |
| Mean age at diagnosis | 60 (SD 14)   |
| Eur                   | 61           |
| Afr                   | 58           |
| Arb                   | 57           |

$\chi^2$  *P*-value < 0.001

<sup>a</sup> Eur, European–American; Afr, African–American; Arb, Arab–American

mean age at diagnosis was 60 years. In situ cases represent 12% of the cohort and 46%, 30%, and 6% had local, regional, or distant disease, respectively, with 6% of an unknown stage.

#### Characteristics at diagnosis

##### Age

The mean ages at diagnosis were 61, 57, and 58 years, for European–American, Arab–, and African–American women, respectively (Table 1). We calculated a log-rank test to compare the distribution of age at diagnosis among the three ethnic groups, which was statistically significant ( $P < 0.001$ ). Each pairwise log-rank test was also significant ( $P < 0.001$ ).

##### Stage

The distribution (number and percent) of SEER staging categories is presented in Table 2a. There was a statistically significant overall  $\chi^2$  for the distributions of stage at

**Table 2a** Distribution of SEER stage at diagnosis for European–, African–, and Arab–American women

| Stage    | Eur          | Afr         | Arb       |
|----------|--------------|-------------|-----------|
| In situ  | 77,341 (12%) | 1,700 (12%) | 209 (13%) |
| Local    | 30,335 (48%) | 5,579 (40%) | 708 (43%) |
| Regional | 18,614 (29%) | 4,599 (33%) | 541 (33%) |
| Distant  | 3,408 (5%)   | 1,152 (8%)  | 92 (6%)   |
| Unknown  | 3,523 (6%)   | 825 (6%)    | 102 (6%)  |

Overall  $\chi^2$  *P*-value < 0.0001

**Table 2b** Odds Ratios (with 95% CI) for SEER stage at diagnosis comparing African–American and Arab–American women individually to European–American women

| Stage    | Eur | Afr              | Arb              |
|----------|-----|------------------|------------------|
| In situ  | 1.0 | 1.01 (0.95–1.07) | 1.05 (0.90–1.21) |
| Local    | 1.0 | 0.74 (0.71–0.77) | 0.82 (0.74–0.91) |
| Regional | 1.0 | 1.20 (1.15–1.25) | 1.18 (1.06–1.30) |
| Distant  | 1.0 | 1.60 (1.50–1.72) | 1.04 (0.84–1.29) |
| Unknown  | 1.0 | 1.08 (0.99–1.17) | 1.12 (0.92–1.38) |

diagnosis by race ( $P < 0.0001$ ). Table 2b gives the unadjusted OR and 95% confidence intervals (CI) for each SEER stage at diagnosis comparing African–American and Arab–American cohorts individually to European–American women. Arab–American women were significantly less likely to be diagnosed with local disease (OR = 0.82; 95% CI 0.74–0.91) and significantly more likely to be diagnosed with regional disease (OR = 1.18; 95% CI 1.06–1.30). Similarly, African–American women were less likely to be diagnosed with local disease (OR = 0.74; 95% CI 0.71–0.77) and more likely to be diagnosed with regional (OR = 1.20; 95% CI 1.15–1.25) and distant disease (OR = 1.60; 95% CI 1.50–1.72).

#### Histology

Table 3a shows the number and proportion of each histological type by race. The overall  $\chi^2$  was significant at  $P < 0.0001$ . The histological tumor type was not significantly different for Arab–American women compared to European–American women. However, notable OR included invasive (OR = 0.86; 95% CI 0.73–1.02), which is borderline significant, and metaplastic (OR = 2.57; 95% CI 0.61–10.76) (Table 3b). African–American women differed significantly from European–American women for

**Table 3a** Distribution of tumor histology at diagnosis for European–, African–, and Arab–American women

| Histology             | Eur          | Afr          | Arb         |
|-----------------------|--------------|--------------|-------------|
| Invasive <sup>a</sup> | 58,469 (92%) | 12,166 (88%) | 1,499 (91%) |
| Metaplastic           | 30 (0.05%)   | 12 (0.09%)   | 2 (0.12%)   |
| Papillary             | 762 (1.2%)   | 305 (2.2%)   | 21 (1.3%)   |
| Squamous              | 58 (0.09%)   | 21 (0.15%)   | 2 (0.12%)   |
| Comedo                | 1,977 (3%)   | 536 (4%)     | 62 (4%)     |
| Medullary             | 1,027 (2%)   | 447 (3%)     | 27 (2%)     |
| Sarcomas              | 160 (0.2%)   | 55 (0.4%)    | 5 (0.3%)    |
| Pagets                | 562 (1%)     | 124 (1%)     | 17 (1%)     |
| Inflammatory          | 569 (0.9%)   | 189 (1.4%)   | 17 (1.0%)   |

Overall  $\chi^2$  *P*-value < 0.0001

<sup>a</sup> Invasive, not otherwise specified

**Table 3b** Odds Ratios (with 95% CI) for histology at diagnosis comparing African–American and Arab–American women individually to European–American women

| Histology             | Eur | Afr              | Arb               |
|-----------------------|-----|------------------|-------------------|
| Invasive <sup>a</sup> | 1.0 | 0.63 (0.59–0.67) | 0.86 (0.73–1.02)  |
| Metaplastic           | 1.0 | 1.84 (0.94–3.59) | 2.57 (0.61–10.76) |
| Papillary             | 1.0 | 1.86 (1.62–2.12) | 1.06 (0.69–1.64)  |
| Squamous              | 1.0 | 1.66 (1.01–2.74) | 1.34 (0.32–5.44)  |
| Comedo                | 1.0 | 1.26 (1.14–1.38) | 1.22 (0.94–1.57)  |
| Medullary             | 1.0 | 2.03 (1.82–2.27) | 1.01 (0.69–1.49)  |
| Sarcomas              | 1.0 | 1.01 (0.83–1.23) | 1.17 (0.72–1.89)  |
| Pagets                | 1.0 | 1.58 (1.16–2.15) | 1.20 (0.49–2.94)  |
| Inflammatory          | 1.0 | 1.53 (1.30–1.81) | 1.15 (0.71–1.87)  |

<sup>a</sup> Invasive, not otherwise specified

invasive (OR = 0.63; 95% CI 0.59–0.67), papillary (OR = 1.86; 95% CI 1.62–2.12), comedo (OR = 1.26; 95% CI 1.14–1.38), medullary (OR = 2.03; 95% CI 1.82–2.27), Paget's (OR = 1.58; 1.16–2.15), and inflammatory (OR = 1.53; 95% CI 1.30–1.81) categories.

#### Marker status

Estrogen-receptor (ER) and progesterone-receptor (PR) status at diagnosis is an important prognostic factor and robust predictor of response to hormonal therapy. The distribution of ER/PR combined status is given in Table 4a. Overall  $\chi^2$  for differences in the distribution of ER/PR between the three racial groups was  $P < 0.0001$ . Arab–American women were more likely, though of borderline significance, to have ER– disease compared to European–American women (OR = 1.17; 95% CI 0.97–1.40), and they were significantly more likely to have ER–/PR– tumors (OR = 1.29; 95% CI 1.08–1.54) (Table 4b). African–American women were significantly more likely at diagnosis to have tumors that were ER– (OR = 2.29; 95% CI 2.15–2.46), PR– (OR = 1.84; 95% CI 1.73–1.96), or both ER and PR negative (OR = 2.09; 95% CI 1.97–2.12) when compared to European–American women. Table 4b depicts the proportion of each ER/PR pair status by race

**Table 4a** Distribution of marker status at diagnosis for European–, African–, and Arab–American women

| Marker  | Eur          | Afr         | Arb       |
|---------|--------------|-------------|-----------|
| ER+/PR+ | 12,926 (64%) | 2,322 (47%) | 382 (63%) |
| ER+/PR– | 2,750 (13%)  | 607 (13%)   | 73 (12%)  |
| ER–/PR+ | 577 (3%)     | 189 (4%)    | 24 (4%)   |
| ER–/PR– | 4,017 (20%)  | 1,710 (36%) | 132 (21%) |

Overall  $\chi^2$   $P$ -value  $< 0.0001$

Note: Frequency missing is 53412 due to data capture not beginning until 1990

**Table 4b** Odds Ratios (with 95% CI) for marker status at diagnosis comparing African–American and Arab–American women individually to European–American women

| Marker  | Eur | Afr              | Arb              |
|---------|-----|------------------|------------------|
| ER–     | 1.0 | 2.29 (2.15–2.46) | 1.17 (0.97–1.40) |
| PR–     | 1.0 | 1.84 (1.73–1.96) | 1.01 (0.85–1.19) |
| ER–/PR– | 1.0 | 2.09 (1.97–2.12) | 1.29 (1.08–1.54) |

and age at diagnosis (dichotomized by age  $< 50$  and  $\geq 50$ ). Of note, the proportion of ER+/PR+ tumors in African–American women  $\geq 50$  is lower than the proportion seen in Arab– or European–American women  $< 50$ .

#### Grade

The distribution of the grade at diagnosis for European–, African–, and Arab–American women is given in Table 5a. The overall  $\chi^2$  for a difference in the distribution between groups was  $P < 0.0001$ . Arab–American women were less likely to have well-differentiated (OR = 0.86; 95% CI 0.71–1.05) and unknown (OR = 0.86; 95% CI 0.78–0.95) tumors at diagnosis than European–American women (Table 5b). They were significantly more likely to have poorly differentiated tumors (OR = 1.25; 95% CI 1.11–1.41). African–American women were significantly less likely to have either well-differentiated (OR = 0.71; 95% CI 0.66–0.77) or moderately differentiated (OR = 0.90; 95% CI 0.86–0.95) tumors as well as tumors with unknown differentiation (OR = 0.78; 95% CI 0.75–0.81). In addition, they were significantly more likely to have poorly differentiated (OR = 1.72; 95% CI 1.65–1.79) or undifferentiated (OR = 1.79; 95% CI 1.52–2.11) tumors.

#### Small tumors with positive nodes

We hypothesize that a surrogate for biologically aggressive disease is a small tumor ( $< 1$  cm) at the primary site with evidence of nodal metastases. Table 6 gives the results of our analysis of small tumors with positive nodes at diagnosis. Both Arab– and African–American women were

**Table 5a** Distribution of grade at diagnosis for European–, African–, and Arab–American women

| Grade            | Eur          | Afr         | Arb       |
|------------------|--------------|-------------|-----------|
| Well             | 4,915 (8%)   | 780 (6%)    | 111 (7%)  |
| Moderately       | 11,302 (18%) | 2,257 (16%) | 317 (19%) |
| Poorly           | 11,023 (17%) | 3,668 (26%) | 343 (21%) |
| Undifferentiated | 511 (0.8%)   | 198 (1.4%)  | 13 (0.8%) |
| Unknown          | 35,863 (56%) | 6,952 (50%) | 868 (53%) |

Overall  $\chi^2$   $P$ -value  $< 0.0001$



**Table 5b** Odds Ratios (with 95% CI) for grade at diagnosis comparing African–American and Arab–American women individually to European–American women

| Grade            | Eur | Afr              | Arb              |
|------------------|-----|------------------|------------------|
| Well             | 1.0 | 0.71 (0.66–0.77) | 0.86 (0.71–1.05) |
| Moderately       | 1.0 | 0.90 (0.86–0.95) | 1.10 (0.97–1.24) |
| Poorly           | 1.0 | 1.72 (1.65–1.79) | 1.25 (1.11–1.41) |
| Undifferentiated | 1.0 | 1.79 (1.52–2.11) | 0.98 (0.56–1.70) |
| Unknown          | 1.0 | 0.78 (0.75–0.81) | 0.86 (0.78–0.95) |

**Table 6** Unadjusted and adjusted OR for probability of being diagnosed with a small tumor (<1 cm) with positive nodes

|     | OR   | 95% CI      | aOR <sup>a</sup> | 95% CI      |
|-----|------|-------------|------------------|-------------|
| Eur | 1.0  | –           | 1.0              | –           |
| Afr | 1.15 | (1.06–1.24) | 1.37             | (1.23–1.52) |
| Arb | 1.18 | (0.96–1.45) | 1.27             | (0.98–1.67) |

<sup>a</sup> Adjusting for age, histology, grade, marker status, year of diagnosis

more likely to be diagnosed with this type of tumor than European–American women; however, the results for Arab–Americans were of borderline significance for both the unadjusted and adjusted analyses. Interestingly, the OR for both Arab– and African–American women increased in magnitude after adjustment.

#### Survival overall and adjusted

Figures 1a–f are the Kaplan Meier plots for overall survival and for survival by SEER stage at diagnosis. In all graphs, Arab–American women have the best survival followed, usually closely, by European–Americans. African–American women have considerably worse survival. In Table 7, the unadjusted and adjusted hazard ratios (HR) from the Cox Proportional Hazards models are presented. Hazard ratios include an interaction term for race-by-age and age-by-marker status, and were adjusted for histology, age at diagnosis, marker status, year of diagnosis, grade, and stage. Commensurate to the graphs, Arab–American women have significantly better survival (HR = 0.83; 95% CI 0.74–0.92) in the unadjusted analysis. The magnitude of the estimate is similar in the adjusted analysis but does not reach significance. Notably, African–American women have a significantly higher mortality than European–American women in the unadjusted (HR = 1.21; 95% CI 1.17–1.25) and more profoundly in the adjusted (HR = 1.93; 95% CI 1.46–2.55) analyses.

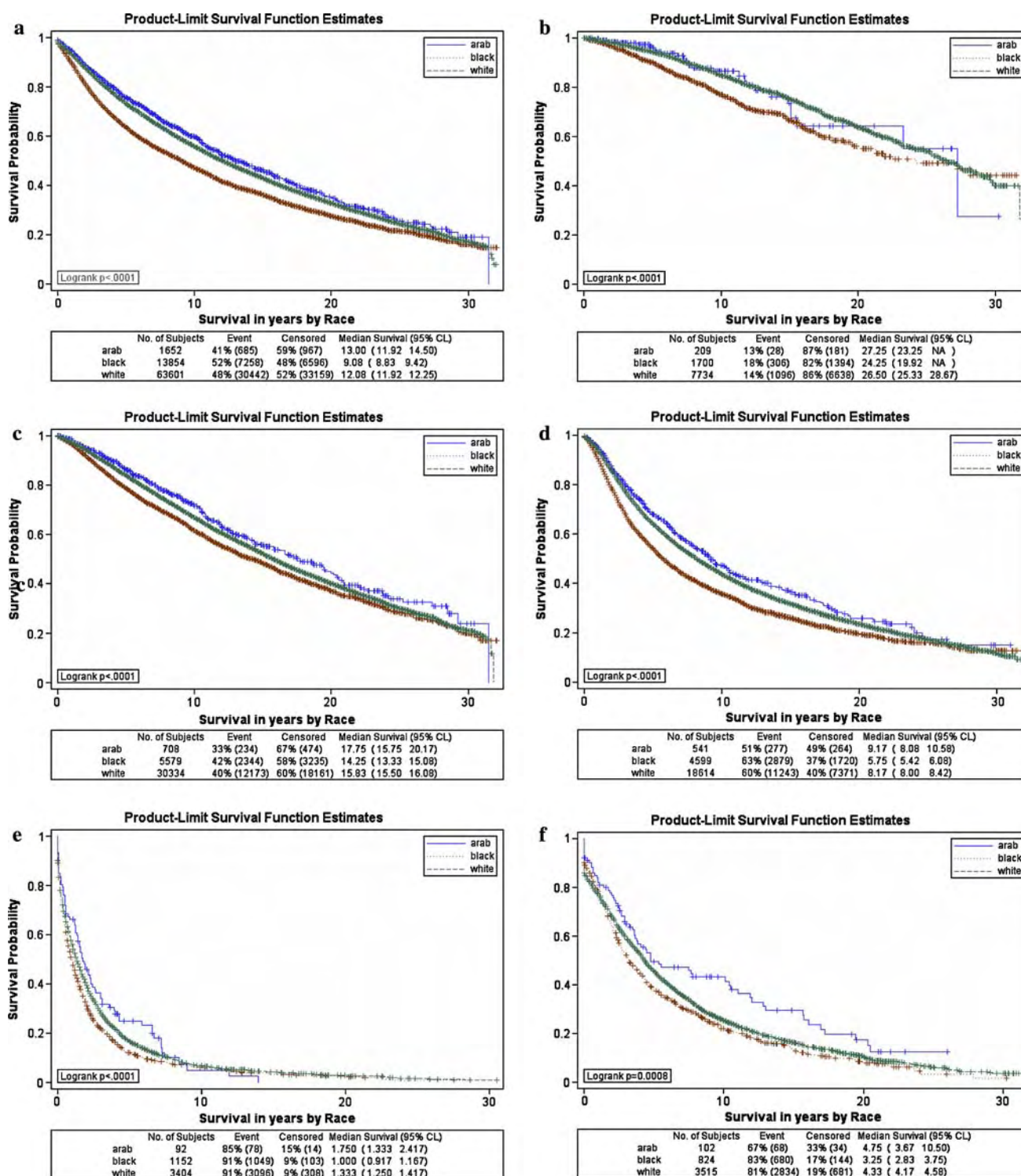
#### Discussion

Data from the Arab world vary regarding the reported breast cancer experience of women. A retrospective review of 292 patients seen at King Fahd Hospital from 1985 to 1995 showed that 78% of patients were younger than 50 at diagnosis and 79% were pre-menopausal [3]. Similarly, in Lebanon, 49% of breast cancer cases diagnosed between 1983 and 1995 ( $n = 2673$ ) were <50 years of age [9]. There is only one oncology clinic in Libya which maintains a tumor registry for all cases receiving consultation. Between 1981 and 1985, breast cancer was the most frequently diagnosed cancer in women, 72% of whom were less than 50 years of age [1]. The data from these studies represent hospital based observations and are thus hard to interpret without additional information. For example, it is possible that only younger women seek treatment for their breast cancer, resulting in a selection bias in the data reported.

In two Egyptian studies, alternative study designs were applied with similar results. Abdel-Rahman et al. [11] used a case–control design to assess epidemiologic features of breast cancer. Results of this study were notable for age at diagnosis and several risk factors. Forty-four percent of cases were diagnosed less than or equal to 50 years of age. Cases were more likely than controls to have a family history of breast cancer, to have a history of radiation exposure, to be working, as well as to have several reproductive factors including higher age at first birth, lower parity, and artificial menopause. Although this study offers some potential explanations for the age distribution of cases, the cases still may have been differentially selected.

Soliman et al. [12] conducted a review of mortality data in Egypt where death certificates are required to receive a burial permit. Records reviewed for the period of January 1, 1992 to December 31, 1996 were compared to US mortality statistics (1991–1995). Results from this population-based study showed a higher age-specific mortality for breast cancer among women less than 40.

Recently, the US NIH/NCI partnered with the MECC to publish cancer incidence data from four MECC countries (Cyprus, Egypt, Israel, and Jordan) [13]. Israel, which has a diverse population, reported age-standardized breast cancer incidence rates of 93 per 100,000 for Israeli Jews and 36.7 for Israeli Arabs. Rates per 100,000 reported for Cyprus, Egypt, and Jordan were 57.7, 49.6, and 38.0, respectively. For comparison, the US SEER rate for all US women over a similar time period was 97.2. Rates for Oman and Kuwait were also available in Volume VIII of the International Agency for Research on Cancer's *Cancer Incidence in Five Continents* [16]. For 1993–1997, the age-standardized breast cancer rate per 100,000 was 12.7 in Oman. The



**Fig. 1** (a) Kaplan-Meier curves by race for overall survival. (b) Kaplan-Meier curves by race for overall survival for in situ SEER stage at diagnosis. (c) Kaplan-Meier curves by race for overall survival for local SEER stage at diagnosis. (d) Kaplan-Meier curves

by race for overall survival for regional SEER stage at diagnosis. (e) Kaplan-Meier curves by race for overall survival for distant SEER stage at diagnosis. (f) Kaplan-Meier curves by race for overall survival for unknown SEER stage at diagnosis

reported age-adjusted breast cancer rate for Kuwaitis between 1994 and 1997 was 32.8 per 100,000. Data quality issues for both countries were noted in the publication.

Using data from the metropolitan Detroit SEER, where an estimated 500,000 Arab-Americans reside, we present the first report of breast cancer characteristics at diagnosis

**Table 7** Cox Proportional HR for overall survival

|     | HR   | 95% CI      | aHR <sup>a</sup> | 95% CI      |
|-----|------|-------------|------------------|-------------|
| Eur | 1.0  | –           | 1.0              | –           |
| Afr | 1.21 | (1.17–1.25) | 2.3              | (1.75–3.03) |
| Arb | 0.83 | (0.74–0.92) | 0.74             | (0.30–1.82) |

<sup>a</sup> Adjusting for histology, age at diagnosis, marker status, year of diagnosis, grade, stage, and interaction between race and age

among Arab–American women. Our results suggest that Arab–American women have a different breast cancer experience than both European– and African–Americans. They were diagnosed at a younger age and had more regional disease and poorly differentiated ER–/PR– disease than their European–American counterparts. Although not statistically significant, there was also a trend observed in our data for Arab–American women to be more likely to have small tumors with positive nodes. Importantly, these differences in disease characteristics, which would suggest poorer prognosis, did not translate into a survival disadvantage. This may reflect the diversity of disease experienced in a genetically heterogeneous group of Arabs in the Detroit area, or it may represent biologically aggressive disease that is responsive to widely accessible treatment; therefore this results in equivalent survival to less aggressive disease more characteristic of European–Americans. With regards to genetic heterogeneity, the term “Arab” refers to an individual from any one of 23 different countries that span geographic and cultural expanses from Mauritania to Oman and from Somalia to Syria and Morocco. The rich cultural diversity of the region includes differences in marriage practices, including currently practiced consanguineous marriages, differences in social behaviors, and a wide-range of environmental exposures including oil production and agricultural practices. An interesting hypothesis that we could not investigate in this analysis is whether the length of residence within the US influences the breast cancer experience of Arab–American women. Other immigration studies have shown that recent migrants maintain the breast cancer risk profile of their native country, but subsequent generations assume the risk profile for the adopted country. SEER does not capture country of birth or date of immigration, which is a limitation in our analysis.

The Arab–American experience for any of the characteristics examined was never as poor as that observed among African–American women. Our study is very robust in distinguishing the relative proportions between all combinations of estrogen and progesterone receptor status, an area of active current interest and investigation. Our results clearly reaffirm that African–Americans are much less likely than either European– or Arab–Americans to

present with ER+/PR+ disease and much more likely to present with ER–/ER– disease; whereas, the mixed phenotypes of hormonal receptor expression status are relatively similar among all the populations. This is a striking finding, especially considering that preponderance of ER–/PR– disease is true in African–Americans for all ages. Several recent review papers have evaluated the potential contributions to breast cancer differences in African–Americans and Caucasians [17–20]. Although it is likely that screening and treatment differences contribute to the disparity in outcomes, it is also clear that differences in tumor biology are important. Polite and Olopade [18] note in their review the evidence of significant tumor biology differences in hormone receptor and HER2 status, grade, S-phase fraction, BRCA-1/2 mutations of unknown significance, and P53. Even when controlling for known differences in tumor biology as well as screening, treatment, and socio-demographic factors, the mortality difference between African–Americans and Caucasians cannot be completely explained. It is likely that as yet unidentified biological differences exist.

We found that delineating the racial distribution of the histologies from the SEER registry was a difficult task, particularly since the analysis includes data from 1973 to 2003, a period during which a major revision of the SEER abstracting guidelines (1988) and changes in the clinical interpretation of the pathology took place. Due to the Tunisian reports, we were interested in examining differences in the proportion of IBC among the three ethnicities. However, since there is not an ICD-O designation for IBC, we used information from the extent of disease codes. Our classification of IBC using this approach is most likely somewhat imprecise. However, assuming non-differential misclassification between ethnic groups; however, we would surmise that the relative differences are accurate, despite the imprecision of the absolute frequency. One other study has used SEER data to evaluate racial differences in IBC incidence and our results generally agree with the previous findings. We found that African–American women were significantly more likely to be diagnosed with IBC (OR = 1.53; 95% CI 1.30–1.81) than European–American women. Our results are consistent with those of Hance et al., who also reported a higher frequency of IBC in African–Americans [21]. However, ours is the first report of the proportion of IBC among Arab–Americans, a subject of great interest, given the increased proportion of IBC in North Africa.

Finally, it is worth noting that if denominator data were available for the Arab community, we would have calculated standardized age-adjusted incidence rates. We suspect that the underlying age distribution structure of the Arab community is younger than that of either the European– or African–American communities in Detroit. Because Arab

ethnicity has been grouped with “Caucasian” in US government population based data collection efforts, we cannot identify the age structure or total population of Arab-Americans in Detroit or elsewhere in the US. Even if we use self-reported country of origin or language spoken at home, the population estimates are most likely an undercount. Our research within this important minority community is significantly hampered by the lack of accurate population estimates and age structure data. The current socio-political climate suggests that further Arab immigration to the US is expected. Detroit alone is anticipating thousands of Iraqi immigrants in the next 12 months from the United Nation’s efforts to resettle Iraqi refugees [22, 23]. Recognition of Arabs as a separate minority group and detailed analyses of their breast cancer burden would allow better population statistics for public health research, policy, and social support services.

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