BREAST CANCER IN YOUNG AGE (≤40 YEARS): THE UNIVERSITY OF TENNESSEE MEDICAL CENTER AT KNOXVILLE 10 YEAR EXPERIENCE

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BACKGROUND

- Breast cancer is most common invasive cancer in women worldwide
- Second leading cause of death from cancer among women
- Approx. 11,000 cases/year in US younger than 40[1]
- 5-7% of all breast cancer cases are < age 40[2]
- Breast cancer in ≤40y/o associated with more aggressive behavior and higher mortality than in older age.[1,3]

[1]*Lee H, Han W. 2014, J Breast Cancer, 17(4): 301-307.*
[2]*Reyna C, Lee M. 2014, J Multidiscip Healthc, 7: 419-429.*
[3]*Pilewskie M, King T. 2014, J Surg Oncol, 110:8-14.*

POOR PROGNOSTIC FACTORS

- "Unfavorable" ER/PR/HER2 phenotype[4]
  - Triple negative (ER-/PR-/HER2-)
  - HER2+ (traditionally considered "unfavorable", but new reports show benefit of Herceptin on overall survival)[4]
- Young age (≤40) at time of diagnosis[2,5,6]
  - More advanced stages
  - Higher grade tumors
  - More lymphovascular invasion
  - More often "unfavorable" phenotype
- Non-Caucasian race[2]

[2]*Reyna C, Lee M. 2014, J Multidiscip Healthc, 7: 419-429.*
[4]*Ross, JS., et al. 2009. The Oncologist, 14(4): 320-368.*
[5]*Slamon, D., et al. 2011. N Engl J Med, 365(14): 1273-1283.*
[6]*Collins, L., et al. 2012. Breast Cancer Res Treat, 131: 1061-1066.*

OBJECTIVE

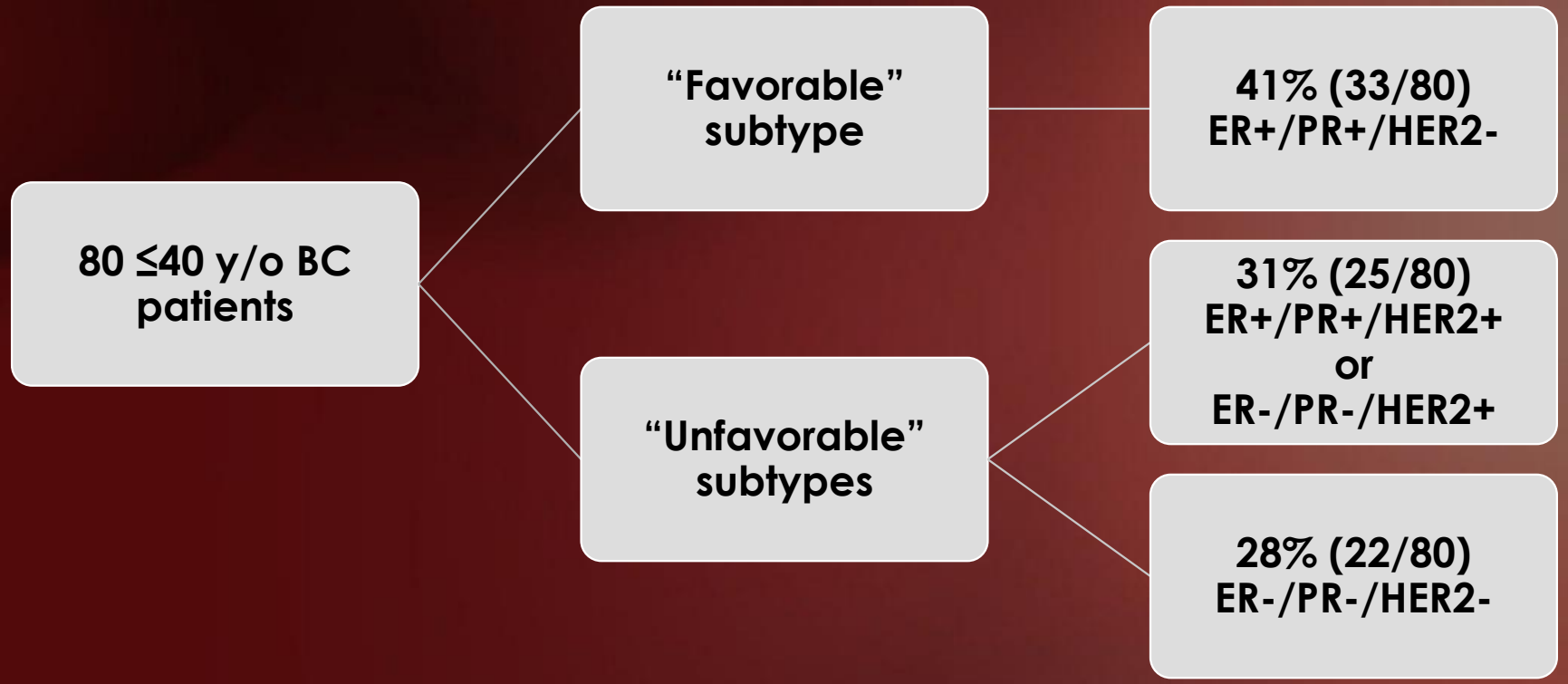
- Young (≤40) Caucasian female patients from our institution
- 10 year period (1/1/1998-7/1/2008), last follow-up date 8/1/2013
- Evaluated prognostic value on overall survival of:
  - Pathologic tumor characteristics
  - ER/PR/HER2 subtypes
  - TNM Stage
- Analyzed type of therapy received

METHODS

- Complete data was available for 80 ≤40 y/o Caucasian females with breast cancer

- Divided into five ER/PR/HER2 groups based on 2011 St. Gallen International Consensus Panel classification system[7]
  - Luminal A like group (ER+ and/or PR+, HER2-, low Ki67)
  - Luminal B/HER2- like group (ER+ and/or PR+, HER2-, high Ki67)
  - Luminal B/HER2+ like group (ER+ and/or PR+, HER2+)
  - Non-luminal HER2+ like group (ER-, PR-, HER2+)
  - Triple negative like group (ER-, PR-, HER2-)

[7]*Goldhirsch A, et al. 2011. Ann Oncol, 22(8):1736-1747.*



Distribution of patients into ER/PR/HER2 subtypes

METHODS (CONT.)

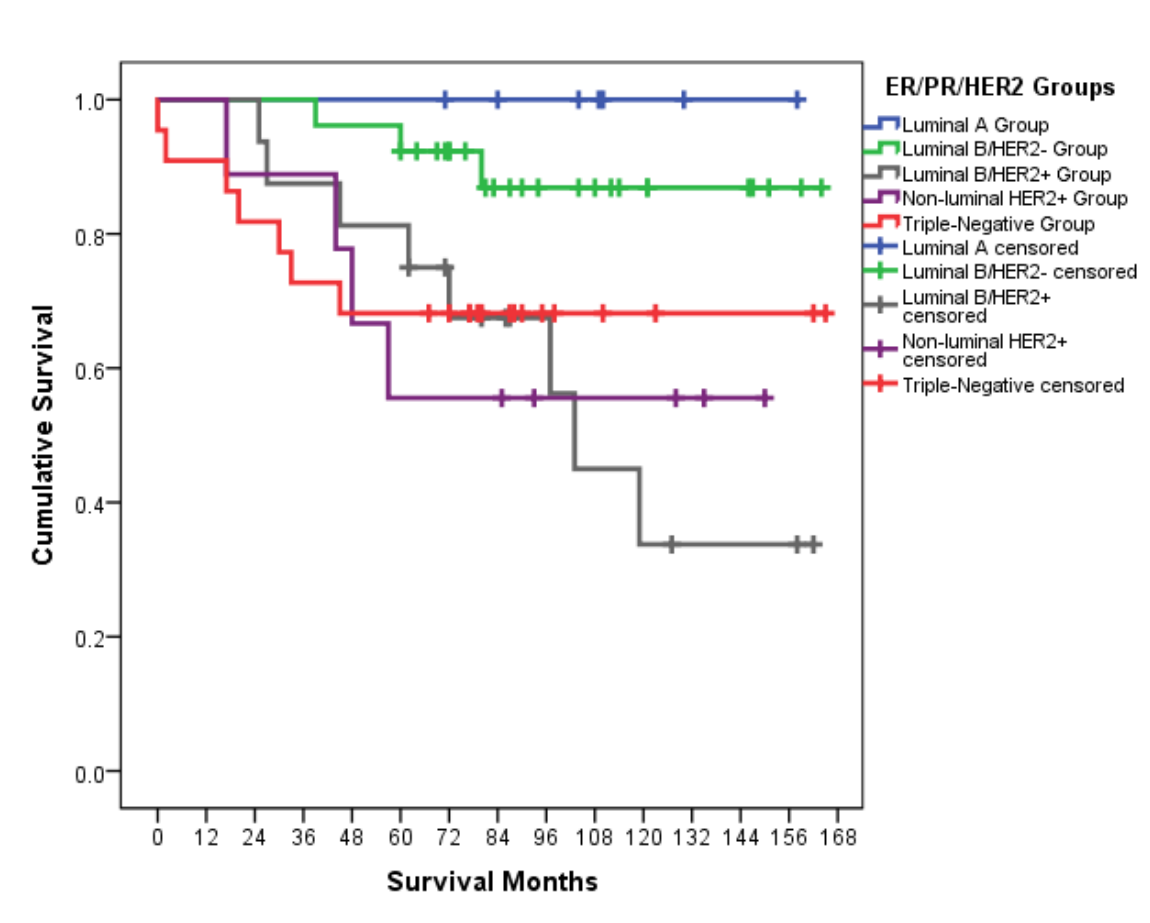
- Frequency statistics, Kaplan-Meier and multivariate Cox regression curves measured impact on overall survival by
  - Pathologic tumor characteristics
  - Effect of ER/PR/HER2 subtype
  - TNM stage

RESULTS

- Majority presented with grade 3 invasive BC (67%) and TNM stage II (50%)

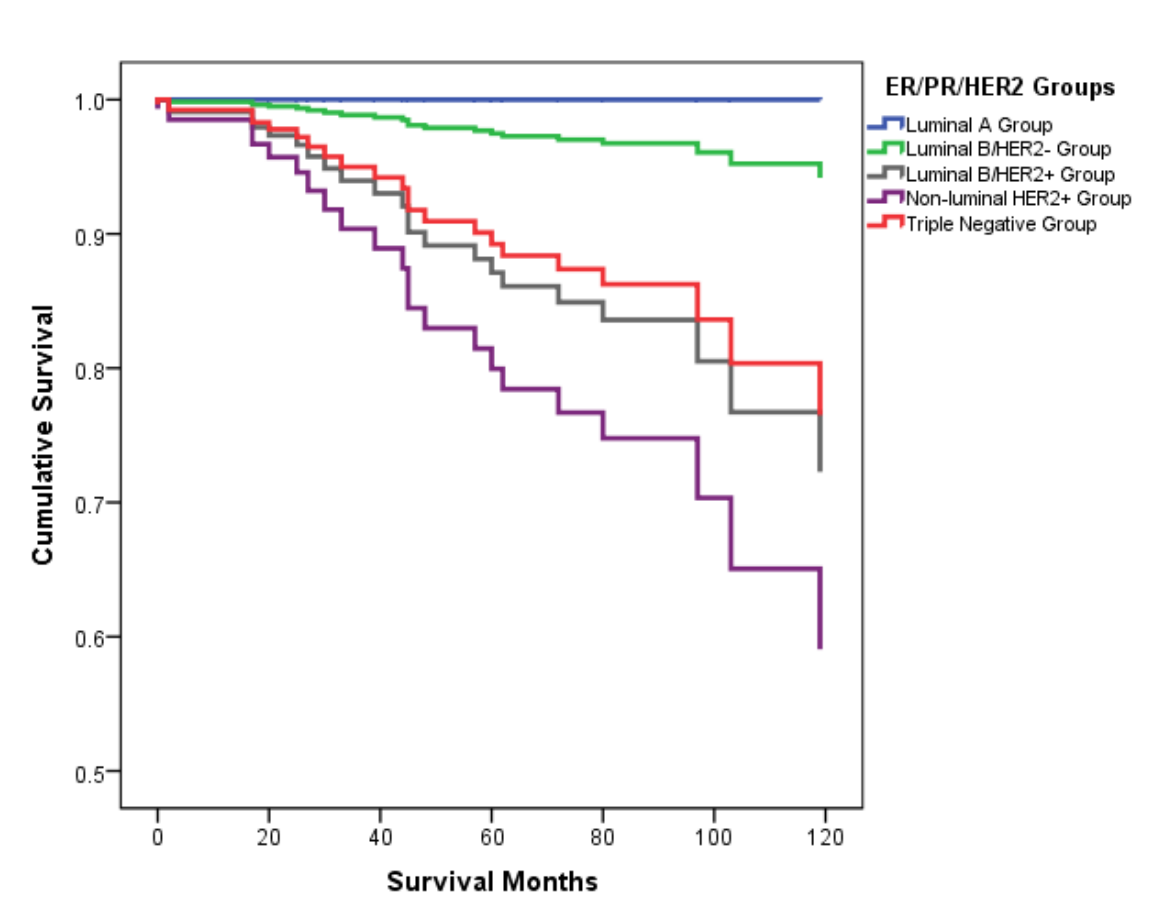
ER+/PR+/HER2- ("favorable")	33/80 (41%)
ER+/PR+/HER2+ or ER-/PR-/HER2+ ("unfavorable")	25/80 (31%)
ER-/PR-/HER2- ("unfavorable")	22/80 (28%)
Mastectomy (modified radical or total)	54/80 (67.9%)
Breast conserving surgery	23/80 (29%)
Post-surgery radiation	37/80 (46.1%)
Post-surgery adjuvant chemotherapy	66/80 (82%)
ER+ patients receiving hormonal therapy	37/49 (76.5%)
Patients with negative lymph nodes	38/80 (47.5%)
Average number of retrieved lymph nodes	12.3

RESULTS (CONT.)



Kaplan Meier curve.
Patients with ER+/PR+/HER2- subtype had significantly better OS than ER-/PR-/HER2- or ER+/PR+/HER2+ (p=.035) in univariate analysis

RESULTS (CONT.)



Cox Regression curve.

When ER/PR/HER2 subtype was controlled for TNM stage and grade in multivariate analysis, only TNM stage was a significant predictor of OS ($p<.001$)

SUMMARY OF RESULTS

- Majority of our young patients presented with high grade and Stage II breast carcinomas
- Treatments:
  - Surgery: 67.9% of patients underwent mastectomy
  - Postsurgical treatments:
    - 46.1% received radiation therapy
    - 82% received chemotherapy
    - 76.5% ER+ received hormonal therapy
- Patients with ER+/PR+/HER2- ("favorable") subtype had significantly better OS than ER-/PR-/HER2- (triple negative) or ER+/PR+/HER2+ (triple positive)
- When ER/PR/HER2 subtype was controlled for TNM stage and grade in multivariate analysis, only TNM stage was a significant predictor of OS

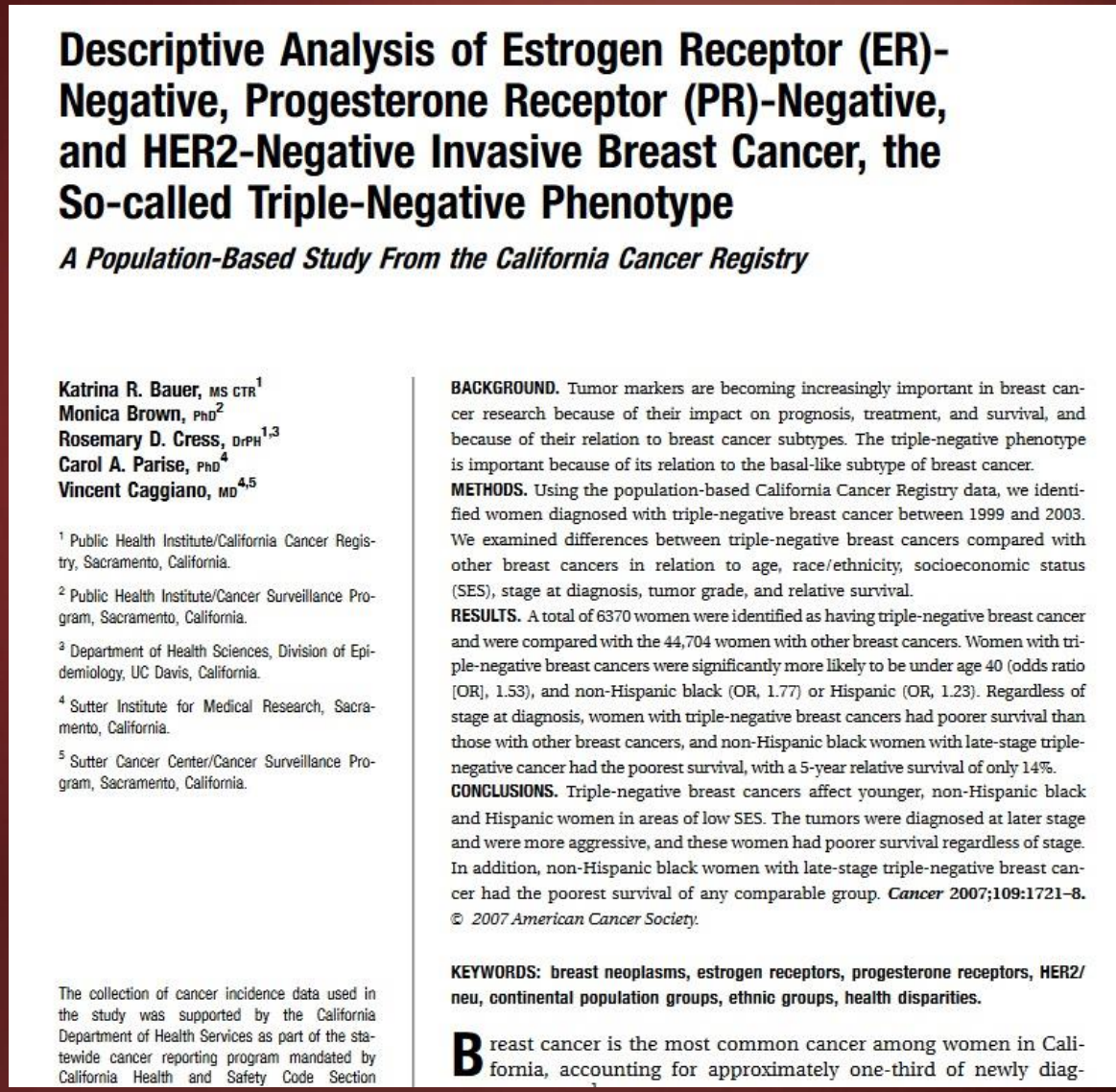
DISCUSSION

- We showed for the first time in this sub-cohort (≤40 y/o) of our Caucasian female breast carcinoma patients that "unfavorable" triple negative ER/PR/HER2 subtype and traditionally considered unfavorable HER2+ subtype were significant predictor of worse overall survival in univariate analysis.

DISCUSSION

- Other researchers:
  - "Triple-negative breast cancers…were more aggressive"
  - "these women had poorer survival regardless of stage"
  - "Triple-negative breast cancers (most commonly) affect younger, non-Hispanic and Hispanic women in areas of low SES."

[6] Bauer K., et al. *Cancer.* 2007;109:1721-1728.



Descriptive Analysis of Estrogen Receptor (ER)-Negative, Progesterone Receptor (PR)-Negative, and HER2-Negative Invasive Breast Cancer, the So-called Triple-Negative Phenotype

A Population-Based Study From the California Cancer Registry

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The collection of cancer incidence data used in the study was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section

BACKGROUND. Tumor markers are becoming increasingly important in breast cancer research because of their impact on prognosis, treatment, and survival, and because of their relation to breast cancer subtypes. The triple-negative phenotype is important because of its relation to the basal-like subtype of breast cancer.

METHODS. Using the population-based California Cancer Registry data, we identified women diagnosed with triple-negative breast cancer between 1999 and 2003. We examined differences between triple-negative breast cancers compared with other breast cancers in relation to age, race/ethnicity, socioeconomic status (SES), stage at diagnosis, tumor grade, and relative survival.

RESULTS. A total of 6370 women were identified as having triple-negative breast cancer and were compared with the 44,704 women with other breast cancers. Women with triple-negative breast cancers were significantly more likely to be under age 40 (odds ratio [OR], 1.53), and non-Hispanic black (OR, 1.77) or Hispanic (OR, 1.23). Regardless of stage at diagnosis, women with triple-negative breast cancers had poorer survival than those with other breast cancers, and non-Hispanic black women with late-stage triple-negative cancer had the poorest survival, with a 5-year relative survival of only 14%.

CONCLUSIONS. Triple-negative breast cancers affect younger, non-Hispanic black and Hispanic women in areas of low SES. The tumors were diagnosed at later stage and were more aggressive, and these women had poorer survival regardless of stage. In addition, non-Hispanic black women with late-stage triple-negative breast cancer had the poorest survival of any comparable group. ***Cancer* 2007;109:1721–8.**

KEYWORDS: breast neoplasms, estrogen receptors, progesterone receptors, HER2/neu, continental population groups, ethnic groups, health disparities.

Breast cancer is the most common cancer among women in California, accounting for approximately one-third of newly diag-

DISCUSSION

- However, in multivariate analysis (controlling for TNM stage and grade), ER/PR/HER2 subtype was not significant predictor of OS, but TNM stage was significant predictor of OS.

- These results are in concordance with our previously published data on the effects of ER/PR/HER2 on OS[8]

[8]Ferguson, NL., et al. *Breast J.* 2013; 19(1)22-30.

The Breast Journal

ORIGINAL ARTICLE

Prognostic Value of Breast Cancer Subtypes, Ki-67 Proliferation Index, Age, and Pathologic Tumor Characteristics on Breast Cancer Survival in Caucasian Women

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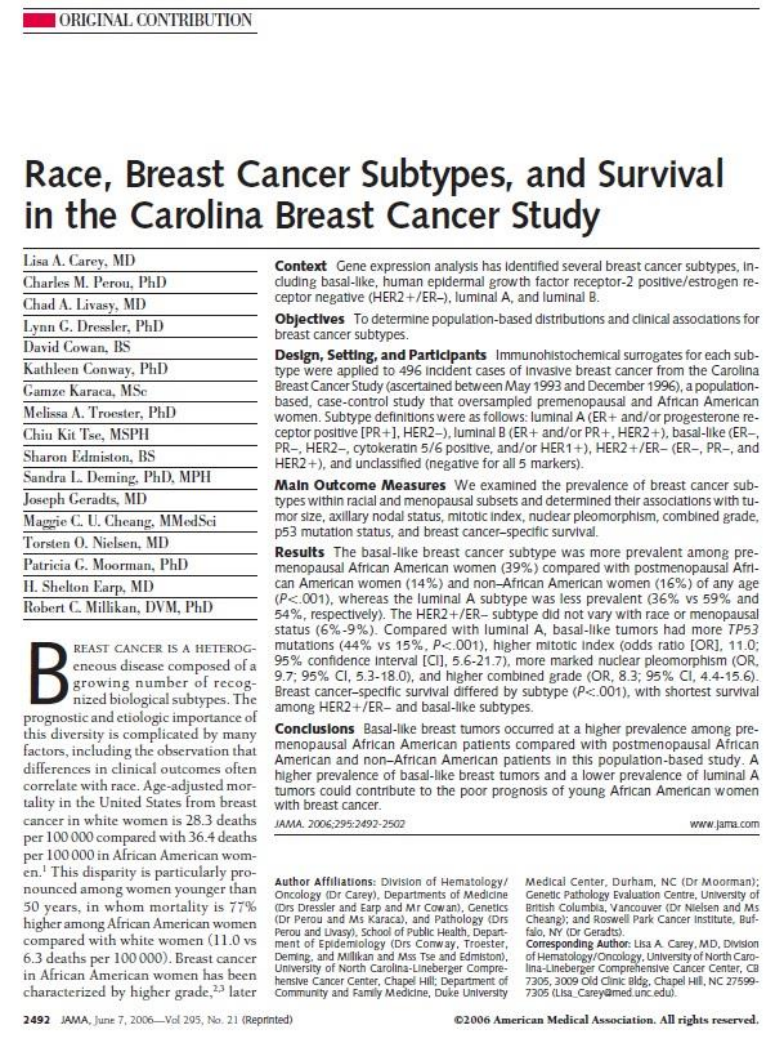
■ **Abstract:** Estrogen receptor (ER), progesterone receptor (PR), and epidermal growth factor receptor 2 (HER2) status are well-established prognostic markers in breast cancer management. The triple negative breast carcinoma subtype (ER-/PR-/HER2-) has been associated with worse overall prognosis in comparison with other subtypes in study populations consisting of ethnic minorities and young women. We evaluated the prognostic value of breast cancer subtypes, Ki-67 proliferation index (Ki-67PI), and pathologic tumor characteristics on breast cancer survival in Caucasian women in our institution, where greater than 90% of the total patient population is white. From 628 new invasive breast cancer cases in our data base (2000-late 2004), 593 (94%) were identified in Caucasian women. ER/PR/HER2 breast cancer subtypes were classified based on St. Gallen International Expert Consensus recommendations from 2011. ER/PR/HER2 status and its effect on survival were analyzed using a Kaplan–Meier curve. ER/PR/HER2 status, grade, tumor-node-metastasis status (TNM)/anatomic stage, and age were analyzed in terms of survival in a multivariate fashion using a Cox regression. Ki-67PI was analyzed between ER/PR/HER2 groups using the Kruskal–Wallis, Mann–Whitney *U*-tests, and 2 × 5 ANOVA. Our results showed that patients with stage IIB through stage IV breast carcinomas were 2.1–16 times more likely to die than patients with stages IA-B and IIA disease, respectively (95% CI 1.17–3.81 through 9.68–28.03, respectively), irrespective of ER/PR/HER2 subtype. Similar effect was seen with T2, N2/N3, or M1 tumors in comparison with T1, N0/N1, and M0 tumors. Chances of dying increase approximately 5% for every year increase in age. There was a significant main effect of Ki-67PI between ER/PR/HER2 subtypes, $p < .001$, but Ki-67PI could not predict survival. In summary, TNM status/anatomic stage of breast carcinomas and age are predictive of survival in our patient population of Caucasian women, but breast carcinoma subtypes and Ki-67 proliferation index are not. ■

Key Words: Breast cancer subtypes, Caucasian women, clinicopathologic characteristics of breast carcinoma, Ki-67 proliferation index, overall survival

DISCUSSION

- Possible causes for the differences in our findings compared to other researchers:
  - Population differences – we only studied young Caucasian females, while other studies included all ethnicities
    - Carolina Breast Cancer Study:
      - Triple-negative BC more common in pre-menopausal African Americans compared to non-African Americans (39% vs 16%)



ORIGINAL CONTRIBUTION

Race, Breast Cancer Subtypes, and Survival in the Carolina Breast Cancer Study

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Context Gene expression analysis has identified several breast cancer subtypes, including basal-like, human epidermal growth factor receptor-2 positive/estrogen receptor negative (HER2+/ER–), luminal A, and luminal B.

Objectives To determine population-based distributions and clinical associations for breast cancer subtypes.

Design, Setting, and Participants Immunohistochemical surrogates for each subtype were applied to 496 incident cases of invasive breast cancer from the Carolina Breast Cancer Study (ascertained between May 1993 and December 1996), a population-based, case-control study that oversampled premenopausal and African American women. Subtype definitions were as follows: luminal A (ER+ and/or progesterone receptor positive [PR+], HER2–), luminal B (ER+ and/or PR+, HER2+), basal-like (ER–, PR–, HER2–, cytokeratin 5/6 positive, and/or HER1+), HER2+/ER– (ER–, PR–, and HER2+), and unclassified (negative for all 5 markers).

Main Outcome Measures We examined the prevalence of breast cancer subtypes within racial and menopausal subsets and determined their associations with tumor size, axillary nodal status, mitotic index, nuclear pleomorphism, combined grade, p53 mutation status, and breast cancer–specific survival.

Results The basal-like breast cancer subtype was more prevalent among premenopausal African American women (39%) compared with postmenopausal African American women (14%) and non–African American women (16%) of any age ($P<.001$), whereas the luminal A subtype was less prevalent (36% vs 59% and 54%, respectively). The HER2+/ER– subtype did not vary with race or menopausal status (6%-9%). Compared with luminal A, basal-like tumors had more *TP53* mutations (44% vs 15%, $P<.001$), higher mitotic index (odds ratio [OR], 11.0; 95% confidence interval [CI], 5.6-21.7), more marked nuclear pleomorphism (OR, 9.7; 95% CI, 5.3-18.0), and higher combined grade (OR, 8.3; 95% CI, 4.4-15.6). Breast cancer–specific survival differed by subtype ($P<.001$), with shortest survival among HER2+/ER– and basal-like subtypes.

Conclusions Basal-like breast tumors occurred at a higher prevalence among premenopausal African American patients compared with postmenopausal African American and non–African American patients in this population-based study. A higher prevalence of basal-like breast tumors and a lower prevalence of luminal A tumors could contribute to the poor prognosis of young African American women with breast cancer.

JAMA. 2006;295:2492-2502 www.jama.com

BREAST CANCER IS A HETEROGeneous disease composed of a growing number of recognized biological subtypes. The prognostic and etiologic importance of this diversity is complicated by many factors, including the observation that differences in clinical outcomes often correlate with race. Age-adjusted mortality in the United States from breast cancer in white women is 28.3 deaths per 100 000 compared with 36.4 deaths per 100 000 in African American women.[1] This disparity is particularly pronounced among women younger than 50 years, in whom mortality is 77% higher among African American women compared with white women (11.0 vs 6.3 deaths per 100 000). Breast cancer in African American women has been characterized by higher grade,[2,3] later

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[9] Carey L., et al. *JAMA* 2006, 295:2492

DISCUSSION

- Other possible causes:
  - Differences in time period of studies – significant improvements in therapies over the last two decades
  - Type of classification system used (St. Gallen vs others)
  - Sample size

CONCLUSIONS

- TNM staging for breast cancer is a relevant prognostic marker in ≤40 y/o Caucasian females with breast carcinoma.
- ER/PR/HER2 status is probably relevant for prognosis, but is likely influenced by other variables.
- Further studies on a larger scale such as NCDB and SEER database analysis are warranted that will systematically analyze impact of race, and different ER/PR/HER2 classification systems on overall survival in this particular age group.
- These analyses should be performed in the same time period as our study was performed.

THANK YOU!

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