Qualitative Age Interactions in Breast Cancer Studies: Mind the Gap

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“Mind the gap” is a warning to subway passengers in London of the sometimes significant space between the train door and station platform. We utilize this phrase to caution researchers to be mindful of the significant gap in our knowledge of age-specific interactions in translational breast cancer research. The relevance of this topic is supported by data showing that many epidemiologic and clinical features of breast cancer demonstrate qualitative age interactions. Here, the term age interaction refers to situations in which breast cancer risk factors, tumor characteristics, and/or clinical trial results differ across age groups. A qualitative age interaction refers to an inverse or crossover effect for different ages. If a qualitative age interaction is suspected, age-related subgroup heterogeneity is likely, and the study should be powered, stratified, or analyzed age specifically to

contrast outcomes between younger and older subjects. Failure to do so may blur important age-specific subgroup effects due to averaging of dissimilar cancer populations.^{1,2}

Peto³ distinguished quantitative (noncrossover) from qualitative (crossover) interactions in randomized clinical trials (RCTs). A quantitative interaction occurs if a treatment outcome varies in magnitude but not in direction for subgroups. A qualitative interaction differs in both magnitude and direction, conferring benefit for one subgroup and harm for another. Although quantitative treatment effects are common, qualitative clinical trial results⁴⁻⁶ are rarely reported (Table 1). Furthermore, qualitative age interactions might be overlooked because age is usually treated as a confounding variable rather than as an effect modifier. As a result, many RCTs adjust or match by age to

Table 1. Qualitative Age Interactions

Parameter	Sample Size	RR _{before crossover age in years}
Epidemiologic risk factor		
Parity v nulliparity ⁷	577 cases, 826 controls	RR _{before 30-44} > 1.0
Obese v lean BMI ⁸	Review	RR _{before 50} < 1.0
Black v white incidence rates ⁹	440,653 cases	RR _{before 40} > 1.0
Tumor characteristic		
Poor v good prognostic factors ¹⁰	242,549 cases	RR _{before 50} > 1.0
Breast cancer outcome ³⁸	1,398	RR _{before 35} > 1.0
Clinical trial results		
Adjuvant Rx for ER+ tumors ⁴	7,631 cases	RR _{before 35} > 1.0
Neoadjuvant Rx (NSABP B18) ⁵	763 preoperative AC, 760 postoperative AC	RR _{before 50} < 1.0
Chemoprevention (fenretinide) ⁶	1,432 cases, 1,435 controls	RR _{before 51} < 1.0

NOTE. Qualitative age interactions are expressed as RRs where one characteristic is compared with a referent characteristic with an assigned RR of 1.0. RR > 1.0 shows increased breast cancer risk or harmful effect while RR < 1.0 shows reduced breast cancer risk or protection compared with the referent characteristic. The crossover age reflects the approximate age of the crossover where RR switches from > 1.0 to < 1.0 or vice versa. RRs in the Table refer to the RR prior to the age of crossover. For example, RR_{before 30-44 years} > 1.0 for parity compared with nulliparity; whereas after age 44 years, RR < 1.0 for parity compared with nulliparity. Parity increases breast cancer risk before ages 30-44 years but is protective thereafter.^{7,12} Obese BMI (body mass index) is protective for premenopausal women before age 50 years but increases risk for postmenopausal women.⁸ Age-specific incidence rates are higher for blacks than whites prior to age 40 years but higher for whites after age 40 years.⁹ Poor prognostic factor characteristics (tumor sizes > 2.0 centimeters, positive axillary lymph nodes, high tumor grade, estrogen and progesterone receptor negative expression) are more common among women before age 50 years, whereas good prognostic factors are more common after age 50 years.¹⁰ Breast cancer outcome (overall recurrence rate and greater risk for developing metastatic disease) is worse among younger (before age 35 years) than older patients, and this difference is not fully explained by greater frequency of adverse prognostic factors.³⁸ Adjuvant systemic therapy is associated with higher rates of relapse for ER+ breast cancers among women before age 35 years than older women.⁴ NSABP B18 showed that neoadjuvant (preoperative) chemotherapy was marginally beneficial among women before age 50 years and the reverse was true for older women.⁵ Fenretinide chemoprevention demonstrated borderline protective effects ($P = .045$) for premenopausal women before age 51 years and harmful effects for postmenopausal women.⁶

Abbreviations: RR, relative risk; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; Rx, treatment; NSABP, National Surgical Adjuvant Breast and Bowel Project; AC, doxorubicin and cytosin.

negate its effect rather than stratify by age to observe its full impact. RCTs also are generally underpowered to analyze age-specific effects. In addition, the age distribution of patients in breast cancer RCTs usually differs from that of patients with comparable tumors in the general community, limiting external validity.

The repeated identification of qualitative age interactions in epidemiologic studies suggests that breast cancer demonstrates age-specific heterogeneity that transcends a simple or single cut point such as menopausal status. For example, parity increases breast cancer risk among women younger than 30 to 44 years but decreases risk among older women (Table 1).^{7,12} Obesity is protective for women younger than 50 years but increases risk thereafter.⁸ The Black to White incidence rate crossover shows that age-specific incidence rates are higher for Black than White women before age 40 years, after which the reverse is true.⁹

Age at diagnosis may reflect established as well as unknown carcinogenic events and/or exposures that occur during a person's life time. Age may even account for some risk conferred by factors that have not yet been identified. Indeed, traditional breast cancer factors account for less than 50% of breast cancer attributable risk.¹⁴ Analyses using novel descriptive and statistical methods also posit that breast cancer may be characterized by early- and late-onset tumor types with modes near ages 50 and 70 years (Figure 1).^{10,15-18} A bimodal characterization also correlates well with the two main clinical biomarkers (estrogen receptor positive [ER+] and HER2+) and/or molecular

breast cancer signatures (luminal and basal-like).¹⁹⁻²¹ However, with few exceptions,²²⁻²⁴ many clinical studies and most molecular studies do not account for the obvious age-related breast cancer differences.²⁵

The identification of a bimodal rather than normal age distribution at diagnosis for a particular breast cancer characteristic raises concerns that the feature identifies a biologically heterogeneous tumor type. Bimodal breast cancer in the general population also contrasts sharply with the restricted age range of many clinical trials where fewer than 10% of participants may be 65 years or older.²⁶ Furthermore, the modal ages of 50 and 70 years do not sharply divide tumors into distinctive categories, but rather reflect central tendencies for the age distributions of two biologically different cancer populations.²⁷ Tumors that develop at extreme ages are likely to demonstrate predominant early- or late-onset phenotypes, but both tumor types span the entire age range with substantial mixing during midlife. Therefore, chronological age is only a crude proxy for breast tissue age.²⁸ Of note, qualitative age interactions and bimodal cancer populations appear to transcend breast cancer, having been described for Hodgkin's lymphoma,²⁹ hairy cell leukemia,³⁰ nasopharyngeal carcinoma,³¹ malignant melanoma,³² high- and low-grade serous ovarian carcinomas.³³

Age, then, may reflect many fundamental and incompletely understood biologic processes. Carcinogenic mechanisms that may increase with age include methylation of CpG islands in promoter regions of tumor suppressor genes, telomere shortening, and genetic instability. In parallel, many age-related changes occur within the systemic milieu such as declines in immune function. Given these data, one might predict that rates of all types of breast cancer would increase monotonically with age and that tumors among older women would be more aggressive. In fact, the opposite is true, breast cancer incidence rates decelerate with aging near Clemmesen's menopausal hook³⁴ and older women generally have more indolent tumors than younger women (Table 1),^{11,25,35} at least before age 70 years.³⁷

Biologic differences for early- versus late-onset tumors also are reflected in different responses to treatments among younger women (Table 1).^{36,38} Women younger than 35 years who express ER+ tumors have worse outcomes than older women with ER+ tumors irrespective of treatment.⁴ This may partly be explained by different patterns of coexpression of key markers at different ages. Neven et al³⁹ reported qualitative age interactions between HER2 and hormone receptor expression. Among HER2 normal tumors, the odds ratio (OR) of being ER+ was 2.6 (95% CI, 1.9 to 3.6) up to age 50 years and age-independent thereafter; the OR of being progesterone receptor positive (PR+) was 2.7 (95% CI, 1.8 to 4.1) up to age 45 and 0.8 (95% CI, 0.8 to 0.9) thereafter. Among HER2+ tumors, the OR of being ER+ and PR+ was 0.8 (95% CI, 0.7 to 1.0) and 0.7 (95% CI, 0.6 to 0.9), respectively. However, an unsupervised analysis of gene expression profiles of ER+ tumors diagnosed in either women 45 years of age or younger or 70 years or older identified six gene clusters, two of which were related to early onset and one to later onset tumors.²² These clusters were unrelated to PR or HER2 status, suggesting biologic complexity related to age at diagnosis that is not completely captured by standard breast cancer markers.

Thus, searching for age-dependent biologic heterogeneity in RCTs would seem to be important. The strength of RCTs derives from their strong internal validity; successful random assignment of subjects coupled with statistical analyses to guarantee comparability among study arms, gives confidence that observed differences in outcomes between groups reflects differences in treatment. However, the

Fig 1. Bimodal age distribution at diagnosis for invasive female breast cancer cases ($n = 94,813$) in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program during the years 1994 through 1997.¹⁶ Kernel density estimation was used to produce smoothed age distributions at diagnosis (or density plots) in single years.¹⁷ The kernel smoother estimated the underlying probability density function for breast cancer incidence by age at diagnosis in single years. The area under the curve represented 100% of the patients with breast cancer. Early- and late-onset modes were observed near ages 50 and 70 years, respectively. Although the relative distributions of the early- and late-onset breast cancer populations have fluctuated over time (likely due to complex interactions between age-related biologic factors and screening and/or birth-cohort phenomena), the modal ages of 50 and 70 years have been robust across molecular portraits, demographic and tumor characteristics.^{10,15,18}

external validity or generalizability of RCTs cannot be assumed since RCTs enroll volunteers who meet inclusion criteria.

The source population for a RCT includes all women potentially eligible for the trial; specifically, patients with breast cancer whose tumors have the characteristics under study. RCTs increasingly evaluate drugs that are directed against specific molecular targets, but the population characteristics of patients whose tumors express these targets are often undefined. Early estimates from high risk cohorts indicated that 30% of breast cancers were HER2+, but these estimates may have overstated the true frequency for HER2 expression in the general population.⁴⁰

Limited access to population-based marker data impairs efforts to assess, the comparability of RCT participants to patients in the community. Generalizability concerns are heightened by data showing that RCT participants are generally healthier, wealthier, younger, and more often white and city dwellers than nonparticipants.^{26,41} Recognition that defining the population-basis for RCTs is important provides the impetus for conducting studies that include molecular analysis of population-based samples.^{13,42} A critical aspect of such studies is their ability to characterize the entire population of both cases and controls, permitting unbiased estimation of incidence rates by marker expression. This research is facilitated by technologies such as tissue microarrays that permit the efficient characterization of large sample sets, improved methods for assaying fixed tissues, and new statistical tools for data analysis. In addition, retrospective marker analysis in older studies may provide insights into tumor behavior before adoption of new treatments.^{42,43} Furthermore, community outcome data may be all that is available to assess new treatments among demographic groups that are under-represented in RCTs.

In conclusion, future breast cancer studies should be designed to permit assessment of age-specific outcomes when possible. The validity of breast cancer RCTs that assess targeted treatments may be strengthened by comparing subject characteristics to those estimated in population-based observational studies. The melding of traditional and novel observational methods can define the population characteristics and suggest hypothesis that would be difficult (if not impossible) to derive in smaller analytic studies and/or RCTs. In addition, differences in the age distributions between RCTs and the general breast cancer population may be masking a fundamentally important biologic variable (aging) that may impact the translation of efficacious treatments to effective patient treatment. This takes on added importance among older patients with breast cancer for whom therapy related complications are as important as cancer cure.⁴⁴ Therefore, the analysis of age-specific effects in RCTs may be a fundamental way to fill the gap of our incomplete understanding of tumor biology and to optimize treatment until more is known of the obligate determinants for breast cancer.

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