EDITORIAL

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Ethnic variation in breast cancer incidence and outcomes—the debate continues

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Ethnic variation in breast cancer outcomes has been known for many decades. Much of the data derives from the US, whereas disparities seen in the United Kingdom are less well studied. Epidemiologic data suggest that the incidence of breast cancer in black women is less than that of white women, while their outcomes are significantly worse (Bowen *et al*, 2006). Despite advances in the treatment and detection of breast cancer, these ethnic disparities have persisted over recent years (Colditz *et al*, 2006). Causative factors are complex and multifaceted but those suggested to be influential include biologic variations in tumour characteristics, differential presentation, variations in co-morbidities, differences in treatment and of course socioeconomic status.

Black women have an increased likelihood of being diagnosed with worse prognosis tumours with a tendency for young black women to have an increased frequency of hormone receptor-negative cancers. There is some evidence that there may be biologic differences in the tumours comparing different ethnic groups. High levels of p53 expression are associated with ER-and PR-negative tumours and have been associated with poorer outcomes—its expression is increased in African-American women when adjustments are made for stage and tumour type (Jones *et al*, 2004). There is also evidence to suggest there is an increased incidence of the mutated proto-oncogene HRAS1 allele in African-Americans.

The characterisation of 'triple-negative tumours' in recent years has identified a wide range of distinct histologic subtypes. The basal subgroup has the shortest relapse-free and overall survival and is more prevalent in African-American women—in particular pre-menopausal women (Carey *et al*, 2006). The reason for this is unclear, however, there are known associations between certain risk factors and disease subtypes. For example, multiparity and young age of first pregnancy protects against luminal breast cancer, whereas it is a risk factor for basal-like breast cancer; conversely early menarche, obesity and breastfeeding were more influential as risk factors for basal-like breast cancer (Millikan *et al*, 2008).

Differences in tumour biology fail to fully account for the ethnic disparities that exist. Identifying where and why there are differences is relevant as it may enable us to better focus on screening of high-risk populations together with variations in treatment for worse-outcome subpopulations. Reported in this journal are the first two UK prospective studies looking at ethnic differences in outcomes and incidence in breast cancer to add further information to the ongoing debate (Copson *et al*, 2014; Gathani *et al*, 2014).

The Million Women Study was designed to establish the impact of hormone replacement therapy on the incidence and outcomes in breast cancer. Published in 2003, it was the largest UK-based prospective study collecting data on hormone replacement therapy and used together with personal and demographic details in women who were aged between 50 and 64 years and were invited for breast screening (Beral *et al*, 2003). Gathani *et al* use these data to further analyse ethnic differences in the incidence of breast cancer. Unique to this study was that prospectively, reproductive and lifestyle information known to influence breast cancer risk were collected. Through Cox-regression models, relative risks for breast cancer incidence were calculated between south Asian, black and white women and the results are published here.

This study recruited 1 048 940 women with data on ethnicity that were followed up for a median of 12.2 years (5877 south Asian, 4919 black and 1 038 144 white women). Baseline characteristics for women based on known risk factors were found to be statistically different in each of the nine domains analysed—age, region, deprivation, age at menarche, childbearing and breastfeeding history, BMI, height, alcohol consumption, use of hormone replacement therapy and family history of breast cancer ($P<0.001$). South Asian and black women had increased levels of deprivation, more children, more likely to have breastfed and less likely to drink alcohol or have a family history of breast cancer. When adjustments were made to determine the relative risk based on age and geographical region both south Asian and black women had a statistically significant reduced relative risk of breast cancer (respectively, RR = 0.82, $P=0.004$; RR = 0.85, $P=0.03$). However, when simultaneous adjustments were made for all nine risk factors, the relative risk for south Asian and black women

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were similar to that of white women (RR = 0.95, $P = 0.5$; RR = 0.91, $P = 0.2$).

With a large enough prospective study population, these results suggest that the differences that are seen may be related to the variable risk factors that exist between ethnic groups. With over a million participants, statistical analysis could be performed to delineate ethnic differences in risk factors and subsequently their influence on incidence of breast cancer. It, however, fails to fully represent the United Kingdom as a whole, as the prevalence of ethnic minorities in the study population was statistically lower than the UK population—thought to be because of the under-representation of London women here. In addition, the study only focuses on 50–64-year-old women that have screen-detected cancers. It is known that black women develop breast cancer at a younger age—a factor this study fails to account for. The conclusions must therefore be taken in context and not inappropriately extrapolated. It may be fair to say from these results that in the screen-detected older population the incidence of breast cancer is similar across ethnic groups when variations in exposure to risk factors are accounted for. It provides an insight into the existence of these variations and prompts further questions that need evaluation, but fails to advance our understanding of why they exist.

In the United States, insurance status and subsequent access to health care are lower in minority groups, and therefore these are important factors in determining the quality of care. This influences the rapidity of diagnosis, access to screening and ultimately availability of treatments. This is less important in these studies within the United Kingdom – where access to health care is free at the point of need – however, other social factors such as poverty, medical literacy and low-educational attainment have also been suggested to influence the ethnic disparities in outcomes. Women of ethnic minorities present at a more advanced stage and this is likely to be related to these socioeconomic factors. Despite this, when socioeconomic status was accounted for, ethnicity persisted as an independent predictor of poor prognosis (Newman *et al*, 2006).

This journal also reports the analysis of ethnic differences by Copson *et al* (2014) from the Prospective study of Outcomes in Sporadic versus Hereditary (POSH) breast cancer study, which is the largest prospective observational study of young patients with breast cancer. This multi-centre prospective observational cohort study recruited 2915 women less than 41 years old including 2690 white, 118 black and 87 Asian women. The results of this support many previous reported findings. However, with small patient numbers compared with many of the larger studies many of the trends failed to reach significance. The study was able to support, with a median follow-up of 5 years, known data that demonstrate that black women have a significantly worse overall survival compared with white women (71.1% *vs* 82.4%; $P = 0.02$) and that distant relapse-free survival was also lower (62.8% *vs* 77% $P = 0.05$).

However, there was a non-significant increased frequency of grade 3 tumours in black patients and a higher proportion of positive nodal involvement when compared with white patients. There was a statistically significant higher frequency of receptor-negative tumours in black than white women (26.1% *vs* 18.6%, $P = 0.04$). Multivariate analyses of these data to adjust for total tumour diameter, grade, nodal status and BMI demonstrated black ethnicity is a significant independent marker of poor prognosis with a HR of 1.50 (95% confidence interval 1.06–2.13; $P = 0.023$) compared with white patients. The authors were not able to account for why this variation existed based on the data they had collated and this independent prognostic effect was only observed in ER-positive tumours.

As it is generally thought that black women have a higher proportion of 'triple negative' tumours conferring to poorer outcomes, it is interesting that this study suggests that black ethnicity is an independent risk factor in ER-positive tumours—this raises the possibility that differences in treatment or in the tumour biology conferring a more aggressive phenotype may be responsible. The study will be analysing tumour samples for further genetic variations and will be reporting on its findings at a later time.

There are a number of studies that have documented differences in treatment received according to ethnicity. Haggstrom *et al* (2005) used the Surveillence, Epidemiology and End Results Medicare population of 22 701 women and analysed differences in care amongst vulnerable populations in the US. They consistently found lower quality care amongst African-American women compared with white women when combining rates of breast-conserving therapy, radiotherapy, surveillance mammography into an overall measure of 'adequate care'. Variations in co-morbidities also contribute to treatment decisions and black patients are known to have increased co-morbidities (Banerjee *et al*, 2007). For example, increased rates of venous thrombo-embolic events in African-American populations limit the use of adjuvant tamoxifen, which is also less well tolerated in black women. The data set is too small to make any firm analysis regarding variations in treatment, however.

The limitation of this study is that despite being prospective, the sample size is low, which may be why it fails to reach statistical significance. Many of the findings are those that are already described in the literature from epidemiologic studies, and therefore it is reassuring that these are supported by data from this study. The analysis was performed on observational data and not powered to identify ethnic differences in outcome.

Both these studies support previous information based on the ethnic differences observed between incidence and outcomes of patients with breast cancer. Gathani's data suggest that differences may be related to the differential exposures to the individual risk factors, which is supported by Copson's data, while also suggesting that black ethnicity is an independent risk factor of poor prognosis. Both are set within the UK NHS that provides universal health care; therefore, they provide an insight into differences in incidence and outcomes of breast cancer that should not be influenced by the ability to pay for care. In this way, these studies undoubtedly add valuable information to the ongoing debate, prompting further questions, suggesting differences may rest, for example, with possible risk factor exposure, but failing to provide any definitive answers in this complex and multifaceted topic.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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