Triple-negative breast cancer: epidemiological considerations and recommendations

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Breast cancer is a major problem for global public health. Breast Cancer is the most common incident form of cancer in women around the world. The incidence is increasing while mortality is declining in many high-income countries. The last decade has seen a revolution in the understanding of breast cancer, with new classifications proposed that have significant prognostic value and provide guides to treatment options. Breast cancers that demonstrate the absence of oestrogen receptor and progesterone receptor and no overexpression of human epidermal growth factor receptor 2 (HER2) are referred to as triple-negative breast cancer (TNBC). There is now evidence emerging from epidemiological studies regarding important characteristics of this group of tumours that carry a relatively poorer prognosis than the major breast cancer sub-types. From this review of available data and information, there are some consistent findings that emerge. Women with TNBC experience the peak risk of recurrence within 3 years of diagnosis, and the mortality rates appear to be increased for 5 years after diagnosis. TNBC represents 10%–20% of invasive breast cancers and has been associated with African-American race, deprivation status, younger age at diagnosis, more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer and BRCA1 mutations. TNBC is regularly reported to be three times more common in women of African descent and in pre-menopausal women, and carries a poorer prognosis than other forms of breast cancer. Although prospects for prevention of non-hormone-dependent breast cancer are currently poor, it is still important to understand the aetiology of such tumours. There remains a great deal of work to be done to arrive at a comprehensive picture of the aetiology of breast cancer. Key recommendations are that there is a clear and urgent need to have more epidemiological studies of the breast cancer sub-types to integrate aetiological and lifestyle factors for prevention of incidence and death, and to have more population-based information of the clinical and biological relevance from cancer registries.

Key words: biology, breast cancer, epidemiology, triple negative

introduction

Cancer is increasingly a global problem [1] and breast cancer is not only the most common incident form of cancer in women worldwide, but is the first or second most common in all regions of the world, and responsible for 1.4 million new cases annually [2]. The incidence of breast cancer is increasing almost everywhere throughout the world, although the mortality rate from breast cancer is declining in many high-income countries [3]. Notable exceptions to this increasing trend in incidence have taken place in the United States where there has been a sharp decrease in incidence from 2002/2003, which occurred in women aged 50–69-years old who predominantly, but not exclusively, had oestrogen-receptor (ER)-positive tumours, and may reflect the early benefit of the reduced use of hormone replacement therapy (HRT) [4].

Only a decade ago, breast cancer was considered a relatively ‘simple’ disease in many respects, with focus essentially on quantifying whether a tumour was, or was not, oestrogen dependent—a situation that had lasted for a century [5]. A quiet revolution has taken place so that in modern times breast cancer is characterized by its molecular and clinical heterogeneity. In this article, the epidemiological studies discussed employed cDNA microarrays [6] and immunohistochemical [7] markers and resulted in breast cancers being classified into five distinct sub-types: ‘luminal A’ [ER positive and/or progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) negative], ‘luminal B’ (ER positive and/or PR positive, HER2 positive), ‘HER2 overexpressing’ (ER negative, PR negative, HER2 positive), ‘basal-like’ [ER negative, PR negative, HER2 negative, cytokeratin 5/6 positive and/or epidermal growth factor receptor positive] and ‘normal breast-like’ tumours.

However, the most modern definition of breast cancer has evolved, with triple-negative breast cancer (TNBC) defined as ER negative, PR negative and lacking overexpression of HER2; luminal-A cancers are defined as ER positive and histologically low grade; luminal-B cancers are also mostly ER positive but may express low levels of hormone receptor and are often high grade; HER2-positive cancers show amplification and high expression of the HER2 gene [8]. Approximately 75% of
TNBCs express basal markers [9, 10] and, consequently, the triple-negative sub-type is frequently, and erroneously, taken as a surrogate marker for the basal-like sub-type. Triple-negative tumours account for ~10–20% of invasive breast cancers [7, 11–13] and this sub-type carries a poorer prognosis than the luminal tumours [6, 7, 12–18].

Large gaps are still apparent in the epidemiology of TNBC, and the current situation will be outlined in this article, and recommendations for priority epidemiological research in this area will also be discussed.

**epidemiology of triple-negative breast cancers**

Perou et al. [19] were the first to describe the various molecular sub-types or molecular profiles of breast cancers. They described four sub-types based on cDNA micro-arrays, including a basal-like sub-type of breast cancer, and noted that most triple-negative tumours clustered in the basal-like sub-type [19]. Since then, multiple studies of gene expression profiling have advanced the understanding of the molecular diagnosis of breast cancer, providing the background for oncologists to use the triple-negative phenotype to describe the basal-like molecular sub-type [20–23]. Of the global breast cancer burden, it has been estimated that ~170 000 are TNBC [23, 24] and are often, but not always, basal-like breast cancer [24–26]; another study has estimated that ~75% are basal-like [12].

**TNBC in African-American and African women**

Carey et al. [12] examined 496 incident cases of invasive breast cancer from the Carolina Breast Cancer Study (1993–1996), a population-based, case–control study that oversampled pre-menopausal and African-American women. They examined the prevalence of breast cancer sub-types within racial and menopausal subsets and determined associations with tumour size, axillary nodal status, mitotic index, nuclear pleomorphism, combined grade, p53 mutation status and breast cancer-specific survival. The basal-like breast cancer sub-type was more prevalent among premenopausal African-American women (14%) and non-African-American women (16%) of any age (P < 0.001), whereas the luminal-A sub-type was less prevalent (36% versus 59% and 54%, respectively). Compared with luminal A, basal-like tumours had more TP53 mutations (44% versus 15%, P = 0.001), 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 sub-type, with the shortest survival among HER2/ER-negatives and basal-like sub-types [12]. The higher prevalence of basal-like breast tumours and a lower prevalence of luminal-A tumours, if a general phenomenon, could contribute to the poorer prognosis apparent among young African-American women with breast cancer.

Using the population-based California Cancer Registry data, Bauer et al. [27] identified women diagnosed with TNBC between 1999 and 2003 to investigate potential differences between TNBC compared with other breast cancers in relation to age, race/ethnicity, socioeconomic status, stage at diagnosis, tumour grade and relative survival. A total of 6370 women were identified as having TNBC and were compared with the 44 704 women with other breast cancers. Women with TNBC were significantly more likely to be under the age of 40, and non-Hispanic black or Hispanic. Regardless of stage at diagnosis, women with TNBC had poorer survival than those with other breast cancers, and non-Hispanic black women with late-stage TNBC had the poorest survival, with a 5-year relative survival of only 14% [27].

Stead et al. [28] identified women with invasive breast cancer diagnosed between 1998 and 2006, with data available on tumour grade, stage, ER, PR and HER2 status, and patient age, body mass index (BMI) and self-identified racial/ethnic group. They recruited 415 patients who were racially and ethnically diverse; 47% were obese and 72% of tumours were ER positive and/or PR positive, 20% were triple negative and 13% were HER2 positive. The odds of having TNBC were threefold higher in African-American women compared with white women. TNBC was equally common in African-American women diagnosed before and after the age of 50 (31% versus 29%), and who were obese or non-obese (29% versus 31%). Considering all patients, as BMI increased, the proportion of triple-negative tumours decreased (P = 0.08). This study indicates once more that black women of diverse background are three times more likely to have TNBC than non-black women, regardless of age and BMI.

Kwan et al. [29] extracted data on 2544 invasive breast cancer cases from two pooled prospective breast cancer studies. Compared with luminal-A cases, triple-negative cases tended to be younger at diagnosis (P < 0.0001) and African-American (OR = 3.14, 95% CI 2.12–4.16), were more likely to have not breastfed if they had parity greater than or equal to three (OR = 1.68, 95% CI 1.00–2.81), and were more likely to be overweight (OR = 1.82, 95% CI 1.03–3.24) or obese (OR = 1.97, 95% CI 1.03–3.77) if premenopausal.

Further confirmation came from Kurian et al. [30] who investigated breast cancer diagnosed in California from 2006 to 2007, which was reported to the National Cancer Institute’s Surveillance, Epidemiology and End Results Programme (N = 40 936). The luminal breast cancer sub-type was found to predominate across racial/ethnic groups, with lifetime risk lowest in Hispanic women (4.6%) and highest in white women (8.1%). HER2-positive breast cancer was found to vary less by race (1.56%–1.91%). The lifetime risk of TNBC was highest in African-American women (1.98%), compared with 0.77% for Asians, 1.04% for Hispanics and 1.25% for whites. Across racial/ethnic groups, nearly half of all luminal breast cancers occur after the age of 70 years. These absolute risk estimates are an excellent contribution to assist understanding of the epidemiology of the ‘new’ sub-types of breast cancer and highlight the utility of a population-based cancer registry in contributing useful knowledge to this entire issue.

Most recently, Amirikia et al. [31], identified 375 761 invasive breast cancers (including 276 938 in non-Hispanic white women and 21 681 in non-Hispanic black women). Non-Hispanic black and Hispanic women tended to be younger than non-Hispanic white women (median ages 57, 54,
and 64 years, respectively). The lifetime incidence rates were higher for non-Hispanic white women compared with non-Hispanic black women and Hispanics; however, for women aged <44 years, incidence was highest among non-Hispanic black women, who also had higher incidence rates of stage III and IV disease and a higher incidence of TNBC in all age categories.

In addition to studies in African-American women, TNBC has also been examined in women with breast cancer in Africa. In the first study of its kind, Huo et al. [32] determined the distribution of molecular sub-types of invasive breast tumours in indigenous black women in West Africa (N = 507). The majority of women presented with large (4.4 cm) high-grade tumours (83%) in advanced stages (72% node positive). The proportions of ER-positive, PR-positive and HER2-positive tumours were 24%, 20% and 17%, respectively. Triple-negativity for these markers was predominant, including basal-like (27%) and unclassified sub-type (28%). Other sub-types were luminal A (27%), luminal B (2%) and HER2 positive/ER negative (15%). The findings were replicated in the second cohort of 129 patients. The unclassified cases could be grouped into a bad prognosis group, with expression of vascular endothelial growth factor, B-cell lymphoma extra-large protein, and Cyclin E, and a good prognosis branch, with expression of B-cell lymphoma protein 2 and Cyclin D1. These findings underscore the urgent need for research into the aetiology and treatment of the aggressive molecular sub-types that disproportionately affect young women in the African diaspora [32].

A study comparing women with breast cancer in the United States (Detroit) and Ghana [33], included 1008 white Americans, 581 African-Americans and 75 Ghanaians; proportions with TNBC were 82%, 26% and 16%, respectively. Among palpable, grade 3 cancers, Ghanaians had the highest frequency of triple-negative tumours (83%) in advanced stages (72% node positive). From the case-only analyses and compared with the ER/PR-positive/HER2-negative sub-type, Trivers et al. [36] reported that women with TNBC were more likely to be obese than normal/underweight (OR = 1.89, 95% CI 1.22–2.92). Regardless of HER2 status, ER-negative/PR-negative tumours were associated with black race, young age at first birth, having a recent birth and being overweight.

While these studies supported an association between TNBC and obesity, Stead et al. [28] reported findings in the opposite direction. They reported that TNBC was equally common in black women diagnosed before and after age 50 (31% versus 29%), and who were obese and non-obese (29% versus 31%). Considering all patients, as BMI increased, the proportion of TNBC decreased (P = 0.08).

**pregnancy and hormonal related risk factors**

Compared with luminal-A breast cancer cases, Kwan et al. [29] found that TNBC cases tended to be younger at diagnosis (P < 0.0001) and African-American (OR = 3.14, 95% CI 2.12–4.16), and were more likely to have not breastfed if they had parity greater than or equal to three (OR = 1.68, 95% CI 1.00–2.81). Shinde et al. [37] reported that compared with women with non-TNBC, women with TNBC had a shorter duration of breastfeeding per child (OR = 0.93, 95% CI 0.90–0.97) and a higher parity (OR = 1.12, 95% CI 1.06–1.20). Using data from 155723 women enrolled in the Women’s Health Initiative, Phipps et al. [38] assessed associations between reproductive and menstrual history, breastfeeding, oral contraceptive use and sub-type-specific breast cancer risk. Reproductive history was differentially associated with the risk of triple-negative and ER-positive breast cancers. Nulliparity was associated with decreased risk of TNBC [hazard ratio (HR) = 0.61, 95% CI 0.37–0.97], but increased risk of ER-positive breast cancer (HR = 1.35, 95% CI 1.20–1.52). Age-adjusted absolute rates of TNBC were 2.71 and 1.54 per 10 000 person-years in parous and nulliparous women, respectively; by comparison, the rates of ER-positive breast cancer were 21.10 and 28.16 per 10 000 person-years in the same two groups. Among parous women, the number of births was positively associated with the risk of TNBC (for three births or more versus one birth HR = 1.46, 95% CI 0.82–2.63) and inversely associated with the risk of ER-positive disease (HR = 0.88, 95% CI 0.74–1.04). The age at

**aetiology of TNBC**

**weight and obesity**

Vona-Davis et al. [35] conducted a retrospective study involving 620 white patients with invasive breast cancer in West Virginia, a population with one of the highest obesity rates in the United States. Patients with TNBC were younger than those with other receptor types (45% and 27%, respectively) and had larger tumours, most notably in the younger women, but small tumours (<2.0 cm) were more often accompanied by lymph node metastases. Obesity was present in 50% of those with TNBC but in only 36% of those with non-TNBC. Lymph node metastases were more frequently associated with T2 tumours in obese patients (P = 0.032) regardless of their receptor status. TNBCs within this white, socioeconomically deprived population, appear to occur more frequently in younger women, with later stage at diagnosis, and in association with obesity, which itself has been associated with a poor prognosis in breast cancer [35].
menarche and age at menopause were modestly associated with the risk of ER positive but not TNBC; breastfeeding and oral contraceptive use were not associated with either sub-type. Although there are very few data available as yet [29, 37, 38] among women with invasive breast cancer, the overall picture of associations between classical breast cancer risk factors and TNBC is still unclear, emphasizing that much work needs to be done.

Two studies have examined the role of oral contraceptive usage in TNBC. Dolle et al. [38] reported that oral contraceptive usage ≥1 year was associated with a 2.5-fold increased risk of TNBC and no significantly increased risk of non-TNBC. Further, the risk among oral contraceptive users conferred by the longer duration of oral contraceptive use and by more recent use was significantly greater for TNBC than non-TNBC. Among women ≤40 years of age, the relative risk of TNBC associated with oral contraceptive use ≥1 year was 4.2, whereas there was no significantly increased risk with oral contraceptive use for non-TNBC among women ≤40 years of age nor for TNBC or non-TNBC among women between 41 and 45 years of age. However, Phipps et al. [39] found that there was no association with TNBC risk and oral contraceptive use.

Kabat et al. [40] studied 148,030 women enrolled in the Women’s Health Initiative in whom there were 300 cases of TNBC and 2479 ER-positive cases diagnosed over a median of 8.0 years of follow-up. Cigarette smoking was not associated with TNBC, whereas alcohol drinkers had reduced risk compared with never drinkers. In contrast, both exposures showed slight positive associations with ER-positive breast cancer. Intakes of wine and hard liquor were also significantly positively associated with ER-positive breast cancer [40]. Kabat et al. [40] concluded that smoking and alcohol consumption are not associated with increased risk of TNBC, but may be modestly associated with increased risk of ER-positive breast cancer.

discussion

Rapid progress in biology has led to the clear demonstration that breast cancer is not a single biological entity and that there are now ways to identify sub-types of breast cancer [7] that are predictive of prognosis, and suggest specific forms of treatment.

The widespread belief that breast and other cancers are rare in low-income regions of the world is a myth [6]. Akarolo-Anthony et al. [41] noted that the probability that a woman who lives up to 65 years of age in Kampala (Uganda) would develop a cancer is only 20% lower than that of her European contemporary [41]. What differs markedly is the probability that the African woman will live up to 65 years of age compared with women in developed countries [2]. The concepts of ‘Risk’ and ‘Burden’ should be clearly differentiated and it should be noted that as life expectancy in Africa increases so too will the cancer burden, and this has already commenced [41]. In these lower-income settings, the case fatality rate is poor in comparison to high-resource countries. Women with breast cancer either present with large, advanced tumours or do not present until the disease is at an incurable stage.

Today it is clear that the entity breast cancer is a global disease and no longer restricted to high-income countries. This is an important step forward and one which highlights the importance of steps that can lead to the prevention of breast cancer itself, prevention of advanced disease and prevention of death in women with breast cancer.

rapid increase in understanding of breast cancer biology

Only a decade ago, breast cancer was considered a relatively ‘simple’ disease in many respects, with focus essentially on quantifying whether a tumour was, or was not, dependent on oestrogen, a situation which had lasted for a century [5]. A quiet revolution has occurred, and breast cancer is now characterized by its molecular and clinical heterogeneity. Homogenous sub-types of breast cancer have been identified, and treatment strategies developed that are more suited to the biology of breast cancer than was possible beforehand. This trend in stratified medicine is one that will continue and has a major potential to bear fruit in the near future.

However, these are still very early days in the development of our understanding of these sub-types of breast cancer, especially from the epidemiological perspective. There are few matters concerning breast cancer sub-types for which there is any strong degree of certainty. For example, TNBC currently constitutes 10%–20% of breast cancer cases—this may reflect a true component of variation, or it may reflect differences in classification of tumours between different centres. There is a potential for confusion between triple-negative and basal-like tumours—not all triple-negative tumours fall into the basal-like sub-type.

The most consistent finding is the threefold increased risk of TNBC in both African-American and African women, although this has been studied less frequently in African women. The reasons for this increase are unclear, and investigation of the underlying determinants, whether genetic or lifestyle, deserve to be a research priority. These differences in tumour biology may be a part of the reason underlying the apparent poorer survival of black women with breast cancer. More work needs to be done in this field of research—initially to make better use of all available data [42] and simultaneously to develop a common approach to future studies in how to deal with various potential confounding factors.

Identification of homogeneous sub-types of breast cancer strongly suggests that there may be different lifestyle factors having different effects on producing the different sub-types. It seems a reasonable basis to believe that tumours that are biologically different could also be aetiology different. As far as the aetiology of TNBC is concerned, there are only a small number of studies undertaken and reported so far. These provide weak associations and findings from one study to another are frequently contradictory.

recommendations

What new actions should be recommended regarding the current state of epidemiological knowledge of TNBC.
specifically? With regards to aetiology and prevention, it is too soon to make any substantial recommendations. It is obvious that more epidemiological studies are needed to understand the new categorization of breast cancers. These must be of the highest quality and involve close collaboration between epidemiologists, pathologists and clinicians. It is essential to separate TNBC from basal-like breast cancer and crucial to use standard definitions of what constitutes TNBC, definitions that lead to reproducibility and concordance. There is also a clear need to progress further in understanding the origins of TNBC. The emerging evidence of a luminal progenitor for TNBC [43, 44] raises important questions about a potential link with hormonal manipulations (such as HRT) on the risk of TNBC.

A major deficiency is the availability of population-based data on the incidence of the sub-types of breast cancer. Part of the evolution of cancer registries must involve collection of cancer data that is relevant to clinical treatment, aetiology and outcome. It could be that survival differences in breast cancer between regions exist that could be explained by differences in the mix of the different sub-types of breast cancer. Without this information being available, there may be a futile search conducted for other false sources of such variation.

All in all, the development of new classifications of breast cancer presents a real opportunity to improve therapies and therapeutic choices and to arrive at a better understanding of the role of lifestyle factors in the aetiology of the disease. This latter presents a major challenge for epidemiology.

disclosure

The author has declared no conflicts of interest.

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