Background: Triple negative breast cancer (TNBC) is an aggressive breast cancer subtype that disproportionately affects women who are African American, younger, or carriers of the BRCA1 gene. No targeted treatments exist for the disease, which has distinct features and presents unique challenges to patients who have been diagnosed with it.

Objectives: TNBC is reviewed in this article according to incidence, tumor grade, stage of diagnosis, biologic and social risk factors, mortality, and treatment.

Methods: Published articles pertaining to TNBC and located through online database searches were reviewed. Articles were selected either because they offered the most current information about TNBC or contributed to the understanding of TNBC.

Findings: Biologic, demographic, and social factors present unique challenges in the treatment of women with TNBC. Knowing about the characteristics of TNBC and the populations who are most at risk for the disease might help healthcare providers better respond to their patients. It may also facilitate responsiveness to patients’ needs and enhance their quality of life.

Triple Negative Breast Cancer Characteristics

Breast cancer is the most common solid malignancy in women aged 20–59 years and the second most common, after lung cancer, in women aged 60 years and older (Siegel, Ma, Zou, & Jemal, 2014). Breast cancer is the leading cause of female cancer deaths in the United States in women aged 40–79 years, as well as the second major cause of female cancer deaths in women aged 20–39 years and in those aged 80 years and older (Siegel et al., 2014). In 2014, 232,670 women in the United States were expected to be diagnosed with breast cancer, and about 40,000 women were expected to die from the disease (Siegel et al., 2014). More than 2.8 million women in the United States are current survivors of breast cancer (American Cancer Society, 2014). The purpose of this article is to examine the incidence, tumor grade, stage of diagnosis, biologic and social risk factors, mortality, and treatment of triple negative breast cancer (TNBC).

Although many subtypes of breast cancer exist, TNBC is defined by the lack of estrogen, progesterone, and human epidermal growth factor receptors. The absence of these three receptors limits treatment options because TNBC does not respond to targeted therapies, such as the use of tamoxifen to treat estrogen receptor–positive tumors (Hugh et al., 2009). Other characteristics of TNBC include high histologic grade, which is indicative of aggressive disease, poor prognosis, increased risk of recurrence within the first three years after diagnosis, and high five-year mortality rates (Arslan, Dizdar, & Altundag, 2009; Chacón & Costanzo, 2010; Ihemelandu et al., 2008; Lara-Medina et al., 2011; Ray & Polite, 2010). The pattern of recurrence for TNBC differs somewhat from that of other breast cancers; the risk of TNBC recurrence is most likely within one to three years.
after the primary surgery, then drops rapidly thereafter (Dent et al., 2007; Fornier & Fumoleau, 2012) (see Figure 1).

Incidence and Mortality

TNBC accounts for about 15% of breast cancers in the United States (Arslan et al., 2009; Chacón & Costanzo, 2010; Kang, Martel, & Harris, 2008; Koshy, Quispe, Shi, Mansour, & Burton, 2010). TNBC is more common in African American women and younger women and particularly common in premenopausal African American women (Amirikia, Mills, Bush, & Newman, 2011; Arslan et al., 2009; Cunningham, Montero, Garrett-Mayer, Berkel, & Ely, 2010; Kurian, Fish, Shema, & Clarke, 2010; Lara-Medina et al., 2011; Lund et al., 2009; Trivers et al., 2009). African American women, regardless of age, have a higher incidence rate of TNBC. In this population, the disease occurs two to three times more frequently than in Caucasian women (Amirikia et al., 2011; Cunningham et al., 2010). Data on TNBC incidence in Hispanic women are limited, and the few available studies have produced inconsistent findings (Giraldo-Jiménez et al., 2012; Lara-Medina et al., 2011; Ray & Polite, 2010).

TNBC is also known to disproportionately affect younger women. Regardless of race, women ages 40 years and younger are almost twice as likely than women aged 60 years and older to develop this subtype of breast cancer (Liedtke et al., 2013). In addition, TNBC has been linked to clinical characteristics, such as increased body weight. However, this relationship is controversial because some studies have shown that the relationship between African American race and TNBC persists after controlling for body weight and body mass index (Stead et al., 2009).

Unlike other types of breast cancer, diagnosis of TNBC tends to occur at more advanced stages and is associated with high rates of lymph node metastasis, distant recurrence, and death within five years of initial diagnosis (Pogoda, Niwińska, Murawska, & Piekowsk, 2013). In addition, metastatic disease in TNBC tends to occur in soft tissues, such as the lungs and brain, rather than in bone (Chacón & Costanzo, 2010). Chemotherapy is the only available treatment option for TNBC, but no standard chemotherapeutic regimen exists for this subtype (Arslan et al., 2009; Chacón & Costanzo, 2010; Koshy et al., 2010).

Biologic Factors

Potential genetic component: The characteristics of TNBC suggest that the disease may have molecular origins that differ from those of other breast cancers (Lund et al., 2009). Stark et al. (2010) compared TNBC prevalence among Caucasian American, African American, and Ghanaian women; Ghana was chosen for the study because many African Americans are believed to have origins in West Africa. Ghanaian women were found to have the highest prevalence of TNBC (82%), followed by African American women (26%) and then by Caucasian Americans (16%) (Stark et al., 2010). TNBC prevalence also was evaluated in women from Senegal and Nigeria. These African women tended to be young, and they often had high-grade tumors and advanced-stage disease at diagnosis (Huo et al., 2009). Results of the study suggest that a genetic link or shared risk factors, such as poverty, may exist among women with TNBC, but more research is needed.

Another genetically based difference is the higher incidence of TNBC in women who are BRCA1 mutation carriers (Brouckaert, Wdiers, Floris, & Neven, 2012). About 75% of women with the BRCA1 gene are diagnosed with TNBC (Brouckaert et al., 2012). The BRCA1 mutation is associated with a deficiency in double-strand DNA repair; this deficiency has implications as a potential target for treatment (Criscitiello, Azim, Schouten, Linn, & Sotiriou, 2012).

Tumor grade: TNBC tumors tend to be poorly differentiated and of a high grade (Ray & Polite, 2010). TNBC was diagnosed 31 times more frequently in grade 3 tumors than in grade 1 or 2 tumors (Ray & Polite, 2010). Racial and ethnic differences are also factors. In African American women, 85% of TNBC cases were diagnosed in grade 3 tumors, compared to 73% of cases in Caucasian women (Cunningham et al., 2010). In addition, Hispanic women diagnosed with TNBC were found to have high-grade tumors, a higher risk of recurrence, and lower survival rates than women with non-TNBC breast cancer (Lara-Medina et al., 2011).

Stage at diagnosis: African American and Hispanic women have been diagnosed more frequently with stage III and IV disease than Caucasian women (Cunningham et al., 2010; Lara-Medina et al., 2011). In most breast cancers, an early-stage diagnosis (i.e., stages I and II) tends to signify better outcomes. However, an early-stage diagnosis of TNBC may not be indicative of a better prognosis (Chacón & Costanzo, 2010). TNBCs are more likely to spread hematogenously, and lymph node status may not be indicative of recurrence (Yaman et al., 2012).

Mortality: Five-year survival rates for women with TNBC tend to be lower than those of non-TNBC breast cancer (Pogoda et al., 2013). Among women with TNBC, African American and Hispanic women have lower disease-free survival and higher mortality rates than Caucasian women (Lara-Medina et al., 2011; Ray & Polite, 2010). The prognosis of TNBC in older women tends to be more favorable than in younger women, despite the likelihood of more aggressive treatment in younger women (Liedtke et al., 2013). Characteristics of TNBC, such as biologic heterogeneity and more advanced stage at diagnosis, may account for its high mortality rate.
Screening and Diagnosis

The National Comprehensive Cancer Network (NCCN) provides guidelines on screening, diagnosing, and treating TNBC, but those guidelines are included within the algorithms for breast cancer in general (NCCN, 2014).

Mammograms are the standard screening tool for detecting breast cancer, yet fewer TNBCs are detected by mammography than other breast cancer subtypes (Dent et al., 2007). TNBC tends to be identified through self- or clinical breast examination rather than screening mammography, suggesting that such tumors occur between or before mammographic screenings and grow rapidly (Billar et al., 2010; Hudis & Gianni, 2011). Yang et al. (2008) found that mammography more successfully identifies masses that have microcalcifications; however, many TNBC tumors are not associated with microcalcifications, limiting mammography detection rates.

Treatment

TNBC represents a subtype of breast cancer that can be organized by genetic, immunohistochemical, or molecular characteristics (Criscitelli et al., 2012; Crown, O’Shaughnessy, & Gullo, 2012; Shastry & Yardley, 2013), but no standard classification system exists, prompting much debate (Criscitelli et al., 2012; Metzger-Filho et al., 2012). Despite this controversy, at least one category is emerging as clinically useful (Chen et al., 2012; Lehmann et al., 2011). Genetic profiles of 587 patients with TNBC from 21 data sets were combined to describe different molecular subtypes of TNBC, resulting in six TNBC subtypes. These classifications consist of two basal-like (BL1 and BL2) subtypes, along with an immunomodulatory subtype, a mesenchymal (M) subtype, a mesenchymal stem-like (MSL) subtype, and a luminal androgen receptor (LAR) subtype (Lehmann et al., 2011). The different TNBC subtypes appear to have varying sensitivities to therapeutic agents. DNA instability demonstrated in the BL1 and BL2 subtypes has been shown to respond to cisplatin, as well as to poly(adenosine diphosphate-ribose) polymerase inhibitors (Shastry & Yardley, 2013). Likewise, the M and MSL subtypes have been reported to respond to NVP-BEZ235 (a dual phosphoinositide 3-kinase/mammalian target of rapamycin inhibitor) and dasatinib (a dual Src/Ab1 kinase inhibitor). LAR subtypes were more sensitive to the androgen receptor antagonist bicalutamide.

The variation in treatment response of TNBC subtypes underscores the need for clinical trials. Clinical trials offer potential treatments that can be useful in managing the disease. However, poor patient participation rates have slowed the advancement of disease understanding (Nass, Moses, & Mendelsohn, 2010). Known barriers to patient participation in clinical trials include a lack of knowledge about them, a negative attitude toward randomization, the potential for adverse reactions, an unease with research, and the complexity of the protocol (Brown et al., 2013; Denicoff et al., 2013; Grand & O’Brien, 2012; Meropol et al., 2007; Mills et al., 2006). Various cultural factors and a history of ethical issues in research involving minority populations add other significant barriers (Denicoff et al., 2013; Somkin et al., 2013). Because TNBC disproportionately affects African American and Hispanic women, addressing the potential barriers that stand in the way of minority populations’ participation in clinical trials is critically important.

Factors Affecting Outcomes

Comorbid Disease

The presence of co-occurring medical conditions may affect the survival rates of patients with TNBC. For example, hypertension, diabetes, and heart disease may have an impact on the outcome of treatments (Ray & Polite, 2010). African American women have higher incidence rates of diabetes, hypertension, and obesity than Caucasian women (Cossrow & Falkner, 2004)—a fact that could influence treatment decision making, treatment, and outcome of treatments (Ray & Polite, 2010). African American women have higher incidence rates of diabetes, hypertension, and obesity than Caucasian women (Cossrow & Falkner, 2004)—a fact that could influence treatment decision making, treatment,
morbidity, and mortality. Braithwaite et al. (2009) conducted a historic cohort study involving 416 African American and 838 Caucasian patients with breast cancer to assess the effect of comorbid conditions on the disparate survival rates observed between African American and Caucasian women. The presence of comorbid hypertension accounted for 50% of the racial disparity for all-cause survival and for 20% of the racial disparity for breast cancer-specific survival.

Social Factors

**Socioeconomic status**: Socioeconomic status (SES) involves a number of variables, including income and education (Siegel, Ward, Brawley, & Jemal, 2011). Low income level was found to be associated with TNBC (Lund et al., 2009; Ray & Polite, 2010; Trivers et al., 2009). Caucasian women in West Virginia with low SES had a higher incidence of TNBC that resembled the incidence rates of TNBC in African American women (Vona-Davis et al., 2008). This study suggests that the association between SES and TNBC may be a strong one, regardless of race.

**Healthcare system and access**: Reduced access to mammography screening and inadequate follow-up of abnormal screening mammograms may account, in part, for African American women's increased morbidity and mortality from breast cancer (Jones et al., 2005). African American women are more likely to experience diagnostic and treatment delays and less likely to receive optimal therapy; in addition, they may not be offered state-of-the-art therapy or refuse recommended treatments (Ray & Polite, 2010). Such imbalances in care may reflect discrimination by the healthcare provider, insurance provider, or healthcare organization, as well as a lack of trust by the African American patient. Hershman et al. (2005) described an association between African American race and premature termination of adjuvant chemotherapy. Communication gaps between physicians and patients may also result in misunderstandings and a failure to adhere to treatment guidelines (Ray & Polite, 2010). The underuse of adjuvant treatment by African American women with breast cancer is also related to a lack of health insurance (Bickell et al., 2006) and to high levels of comorbidity.

**Implications for Practice**

- Understand the specific factors related to triple negative breast cancer (TNBC) to help tailor information and care to each patient.
- Pay attention to each patient’s age, race, treatment options, and prognosis, among other factors.
- Be sensitive to the potential needs and coping styles of patients within the populations disproportionately affected by TNBC.

**Genetic testing and decision making**

TNBC disproportionately affects African American women and young women, as well as carriers of the **BRCA1** mutation. A standard treatment protocol has not been established. However, recently discovered TNBC subtypes have responded to various therapeutic agents, emphasizing the need for clinical trials to generate evidence for practice. Healthcare providers should be aware of TNBC and the populations most likely to be affected by it to provide individualized care.

**Conclusion**

TNBC is a breast cancer subtype that disproportionately affects African American women and young women, as well as carriers of the **BRCA1** mutation. A standard treatment protocol has not been established. However, recently discovered TNBC subtypes have responded to various therapeutic agents, emphasizing the need for clinical trials to generate evidence for practice. Healthcare providers should be aware of TNBC and the populations most likely to be affected by it to provide individualized care.

**References**


