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Population and target considerations for triple-negative breast cancer clinical trials

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Abstract

Triple-negative breast cancer (TNBC) is an aggressive disease subtype that has a poor prognosis. Extensive epidemiological evidence demonstrates clear socioeconomic and demographic associations with increased likelihood of TNBC in both poorer and minority populations. Thus, biological aggressiveness with few known therapeutic directions generates disparities in breast cancer outcomes for vulnerable populations. Emerging molecular evidence of potential targets in triple-negative subpopulations offers great potential for future clinical trial directions. However, trials must appropriately consider populations at risk for aggressive subtypes of disease in order to address this disparity most completely. New US FDA draft guidance documents provide both flexible outcomes for accelerated approvals as well as flexibility in design with adaptive trials. Careful planning with design, potential patient population and choices of molecular targets informed by biomarkers will be critical to address TNBC clinical care.

Keywords

clinical trials; disparities; triple-negative breast cancer

Triple-negative breast cancer (TNBC) is diagnosed when the estrogen receptor (ER), progesterone receptor (PR) and HER-2 biomarkers are determined to be negative and, in this setting, chemotherapy has been the primary therapeutic approach, particularly in the case of positive lymph node status. Recent work has identified six molecular subtypes of TNBC with varying sensitivities to known chemotherapies. Additional preclinical work has established numerous biomarkers and potential therapeutic targets such as phosphate and tensin homolog and INPBB4, components of the PI(3)K and RAS–RAF–MEK pathways, KRAS, BRAF and EGF receptor (EGFR), FGF receptor (FGFR) 1, FGFR2, IGF receptor 1, KIT, MET and alpha-type PDGF receptor and HIF1- α /ARNT. It is clear from all of these

efforts that there is no one primary target that will be able to adequately target the majority of TNBC patients due to the heterogeneity of this disease.

Epidemiological evidence has demonstrated that breast cancer subtypes are most clearly associated with race, socioeconomic status and other environmental and lifestyle exposures such as stress, diet, physical activity, alcohol consumption, residential neighborhood disadvantage and occupation. Effectively, African-American women are more likely to develop TNBC than white women. Similarly, those of lower socioeconomic classes have a higher likelihood of developing TNBC than those of higher socioeconomic standing. The challenge for the cancer research community is to determine how to utilize modifiable components of these determinants in promoting cancer prevention and control strategies, for promoting appropriate inclusiveness of populations in clinical trials, and for the potential identification of therapeutic directions.

In 2012, the US FDA released a draft guidance outlining the usage of pathological complete response (pCR) as the primary outcome for high-risk early-stage neoadjuvant breast cancer clinical trials in order to promote approvals of promising therapies based on accelerated approval regulations (part 314, Code of Federal Regulations, title 21 [H] and title 601 [E]) [201]. This guidance, along with draft guidance on the use of adaptive clinical trial designs, paves the way for the development of novel clinical trial designs for targeted therapies in TNBC. Multidisciplinary efforts will be required in order to assure that design, access to populations, in-depth knowledge of available and appropriate targets and rigorous analytical approaches can be jointly applied to assure successful trial completion.

Molecular heterogeneity of breast cancer

It has been more than a decade since the seminal articles defined unique molecular subtypes of breast cancer based on transcript profiling and the resultant clinical implications that have emerged [1–3]. Disease subclassification has been practice changing in that targeted therapies can be utilized for patients with breast cancer positive for ER, PR or HER-2 gene amplification tumors [4,5]. TNBC is diagnosed when these three markers are determined to be negative, and in this setting chemotherapy has been the primary therapeutic approach, particularly in the case of positive lymph node status [4]. Specifically, triple-negative status is accurately determined, according to the American Society of Clinical Oncology and College of American Pathologists guidelines, as those breast cancers displaying an absence of the ER and PR along with HER-2 negativity defined either by immunohistochemical tissue staining or by the ratio of HER-2 gene copy number to centromere of chromosome 17 < 2 by FISH assay [6,7]. The larger subtype within TNBC is called basal-like breast cancer (BLBC), characterized by expression patterns of CK5/6, CK14, CK17, vimentin, P-cadherin, EGFR and caveolins 1 and 2, among others [8]. Currently, there is no widely accepted assay for determining BLBC, and there is imperfect concordance of TNBC and BLBC, reflecting unresolved heterogeneity of the disease classification [1–3].

Pietenpol *et al.* used archived gene expression data to establish and validate subtypes within TNBC [9]. Based on a training set of 386 arrays and a validation set of 201 arrays, their analysis yielded six TNBC subtypes; two basal-like (BL1 and BL2), an immunomodulatory, a mesenchymal, a mesenchymal stem-like and a luminal androgen receptor subtype. Utilizing these expression-based subtypes they characterized TNBC cell lines and demonstrated that these TNBC subtypes exhibit differential sensitivity to select chemotherapy agents in xenograft experiments. Chiosis *et al.* found that a number of known receptors (EGFR, IGF1R, Her3, c-Kit and Raf-1) formed a complex in TNBC with PU-H71-bound HSP90 and also identified RAF/MEK/ERK pathway components that were previously not reported to be bound to HSP90 [10].

The Cancer Genome Atlas Network recently published an analysis of primary breast cancer based on genomic DNA copy number arrays, DNA methylation, exome sequencing, mRNA arrays, miRNA sequencing and reverse-phase protein arrays [11]. In these integrated data, a molecular similarity of BLBC and serous ovarian cancer was identified, in particular loss of TP53, RB1 and BRCA1 and amplification of MYC. These data suggest common therapeutic approaches of platinum analogs and taxanes in BLBC and serous ovarian cancer. The data also demonstrate the heterogeneity of TNBCs, with approximately 20% with germline or somatic mutation of *BRCA1* or *BRCA2*. Some of the additionally identified targets included phosphate and tensin homolog and INPBB4, and some components of the PI(3)K and RAS-RAF-MEK pathways exhibited amplification. Some other potential identified targets include KRAS, BRAF and EGFR [12,13]. Other receptor tyrosine kinases that show potential as drug targets and that were amplified in some basal-like cancers include FGFR1, FGFR2, IGF receptor 1, KIT, MET and α -type PDGF receptor, and HIF1- α /ARNT. However, there was no highly prevalent single target identified.

A recent Phase III trial failed to demonstrate a survival benefit in TNBC of the putative PARP inhibitor iniparib [14] following a successful Phase II trial [15]. However, new evidence has emerged that iniparib does not function as a PARP inhibitor [16], so more research of PARP as a molecular target is required. In addition, critical structural identification on PARP-1 and its domain interfaces required for DNA-dependent activity presents potential targets for design of novel PARP-1 inhibitors [17].

Epidemiological evidence of disparities in breast cancer & differential molecular subtype

Breast cancer continues to be the highest incident cancer among women in the USA. It is estimated that approximately 226,870 new breast cancer cases will be diagnosed among women in the USA in 2012. In addition, almost 39,510 deaths will be attributed to the disease [18]. Numerous studies have shown that although African-Americans have a lower incidence rate of breast cancer compared with whites, they have the highest mortality rates due to breast cancer compared with other racial groups. In addition, African-Americans have benefited the least from the overall decreasing trend of breast cancer mortality in recent years that has resulted from early detection and treatment [19]. Thus, significant racial disparities in breast cancer outcome continue to exist [20]. Table 1 presents a summary of the studies revealing evidence of disparities in breast cancer and its relation to tumor size, stage, grade and receptor status. While there are underlying disparities related to other features, our focus here is on the potential biological and ultimately therapeutic targeting of these disparities.

Improvements in both early detection and screening technologies have contributed to the overall decline in breast cancer mortality rates in recent years. In addition, effective systemic therapy options have been developed for the molecular marker expression of individual tumors. However, these improvements in treatment methods will lead to better health outcomes only if the disease is detected in its early stages. Tumors that are detected at advanced stages are more likely to be associated with adverse outcomes [21].

Hormone receptor status, specifically ER and PR status, has been found to be an effective prognostic indicator for overall breast cancer survival and treatment. Hormone receptor-negative tumors are more likely to be associated with recurrence and poorer survival compared with hormone receptor-positive tumors. Hormone receptor status will also indicate the effectiveness of endocrine therapy. Hormone receptor-positive tumors have been found to respond more appropriately than hormone receptor-negative tumors to hormonal treatment. Distinct differences in hormone receptor status have been shown to

vary by race. Studies have found that ER-negative tumors are more frequently found among African-American women compared with white women [22–25]. These tumors are also of higher nuclear grade [26]. Tumors that do not express ER, PR and HER-2 are known as triple negative and are significantly more aggressive compared with the other subtypes. This clinically challenging tumor subtype is diagnosed more frequently among African-American women compared with white women [23–25]. It has been reported that in the USA, African-American women are twice as likely to be diagnosed with these tumors compared with white women, and that African-American women are over-represented in breast cancer patients diagnosed under the age of 45 years. The highly aggressive nature of these tumors and the lack of effective treatments contribute to the poorest overall survival observed among African-Americans [26].

A large part of the racial disparities related to breast cancer mortality can be attributed to the more advanced stage of diagnosis often observed among African-American women compared with white women [27]. A more advanced or later stage of cancer at diagnosis results in limited treatment options and reduced likelihood of survival compared with cancers diagnosed at earlier stages of disease [28]. The survival rates for distant, regional and localized stage tumors have been approximated as follows: 23.3, 83.5 and 98.3%, respectively [29]. It has consistently been shown that breast cancers among disadvantaged populations, such as racial and ethnic minorities, are more likely to remain undetected until the cancer has reached later, more advanced stages of disease [28]. Although overall breast cancer incidence is higher for white women, African-American and Hispanic women are disadvantaged regarding stage at diagnosis and survival [30]. In the USA, African-American women are more likely than white women to be diagnosed with regional or distant breast cancer [31]. McBride *et al.* demonstrated that tumor size is increased in African-American patients in multivariate models controlling for age and nodal status [26]. Similarly, the presence of positive nodes is elevated in African-American patients, demonstrated in multivariate analysis controlling for age and tumor size as well as ER status and other factors. These within-stage differences may contribute to the higher mortality rate found among African-Americans compared with white women [31].

Race is considered to be a significant independent risk factor for breast cancer outcomes. These racial differences in disease are considered to be multifactorial in nature since environmental as well as genetic factors are responsible for the biology of the observed tumors [25]. Several risk factors have been hypothesized in the literature to cause these racial disparities in female breast cancer biology and include socioeconomic status, stress, diet, physical activity, alcohol consumption, characteristics of neighborhood of residence and occupation [28–30,32–41].

Cho *et al.* found that the concentration of and increases in immigrant populations within neighborhoods influenced diagnosis of late-stage breast cancer [33]. According to Dai, residence in areas with African-American segregation significantly increased the risk of late-stage diagnosis [34]. Keller *et al.* found racial disparities with regard to breast cancer stage at diagnosis throughout the USA, independent of geographic location in the country. Compared with white women, nonwhite women presented with later stage disease in all geographic areas of the country examined [37].

Several studies have indicated that differences in tumor grade due to socioeconomic status contribute to outcomes disparities [20,42–44]. Ademuyiwa *et al.* also reported that lower serum vitamin D concentrations may be associated with higher-grade tumors [20]. Thus, the higher-grade tumors diagnosed among African-American women may be indicative of lower vitamin D levels among these women [20].

Desantis *et al.* concluded that African–American women were almost twice as likely to be diagnosed with large tumors compared with white women and were more likely to be lymph node-positive [43]. In addition, it was reported that insurance status and area-level educational attainment accounted for almost 31% of the excess risk of being diagnosed with a larger tumor [43]. Kuzmiak *et al.* also found a significant effect of insurance status on tumor size [44]. McBride *et al.* found that African–American women were 24% more likely to have at least one positive lymph node when compared with white women [26].

There is overwhelming evidence that racial disparities exist in relation to hormone receptor status [15,20–23,25,27,42,43–63]. Studies examining socioeconomic status as a cause of racial disparities in hormone receptor status concluded that areas of high poverty had a greater prevalence of hormone receptor-negative tumors compared with areas of low poverty. In addition, studies examining risk of triple-negative subtypes concluded that the risk of diagnosis with this subtype is greatest among African–American women compared with other races. Parise *et al.* examined various breast cancer subtypes in their study and found that the subtypes with the worst overall survival were all ER-negative [15]. In addition, the majority of women diagnosed with triple-negative tumors in their study were non-Hispanic African–American or Hispanic and of the lowest socioeconomic status group [64]. It is evident that the underlying tumor biology of hormone receptor-negative breast cancers has multiple potential causes, is related to socioeconomic status and race, and represents subtypes that currently pose clinical challenges.

Several studies have concluded that the characteristics of one's neighborhood of residence can have significant effects on racial disparities in breast cancer biology outcomes. The levels of affluence and poverty in a neighborhood are significantly associated with distant metastasis at diagnosis [30]. In addition, it was found that community change also affected the likelihood of late-stage diagnosis. Cho *et al.* found that women residing in neighborhoods that experienced more disadvantage over time experienced additional risk of late-stage diagnosis. Increasing concentrations of immigrant populations also contributed to this additional risk. It is possible that changing population dynamics influence the likelihood of late-stage diagnosis through increasing the burden on healthcare facilities to supply adequate healthcare to residents [33].

Racial segregation in neighborhoods has also been identified as a cause of racial disparities in breast cancer biology outcome. Segregation limits the potential for employment, education and healthcare access for communities. Thus, segregation influences disparities through resulting low socioeconomic status and lack of access to adequate healthcare resources. Socioeconomic barriers in highly segregated neighborhoods, such as lack of car ownership, can impact a woman's ability to receive a breast cancer diagnosis when the tumor is still in its early stages. In addition, Dai reported that residence in highly segregated neighborhoods is associated with the absence of personal health promotion behaviors [34]. Thus, residential segregation is a major factor associated with late stage diagnosis among African–American women due to poor mammography access and personal beliefs regarding health promotion [34].

Socioeconomic status has been shown to be strongly associated with breast cancer biology. Desantis *et al.* found race, insurance status and area-level educational attainment to be strongly associated with five different prognostic factors for breast cancer: hormone receptor status, grade, tumor size, lymph node status and metastasis [43]. The associations between socioeconomic characteristics and stage at diagnosis or tumor size may be explained by inadequate access to screening and lack of timely follow-up. Those who live in areas of low socioeconomic status are less likely to receive regular screening services, resulting in advanced stage at diagnosis. African–American women are more likely than white women

to be of lower socioeconomic status, uninsured and are less likely to receive timely screenings. Although many studies have focused on disparities in stage at diagnosis and tumor size, we still lack sufficient knowledge regarding the effect of socioeconomic status and racial differences in tumor grade and hormone receptor status. It has been hypothesized that these racial disparities in tumor grade and hormone receptor status may be due to lifestyle-related factors such as obesity, which is more prevalent among African-American women compared with white women [43,52,61,63,65,66].

Emerging evidence also demonstrates that oral contraceptive use, reproductive and menstrual history and breast-feeding may be associated with breast cancer subtypes [67,68]. Nulliparity is associated with decreased risk of TNBC.

Thus, there is a wealth of epidemiological evidence of the potential underlying determinants of the predilection of TNBC in vulnerable populations. The challenge is for the cancer research community to determine how to utilize modifiable components of these determinants in promoting cancer prevention and control strategies, for promoting appropriate inclusiveness of populations in clinical trials, and for the potential identification of therapeutic directions. An additional challenge comes from the changing definitions of TNBC and other subtypes over time, as knowledge and techniques improve, and the fact that historic cohorts may have misclassification of patients into subtypes, further confounding efforts to understand potential risks.

Ongoing clinical trials in TNBC

In November of 2012, a search of clinicaltrials.gov revealed 81 ongoing interventional clinical trials in TNBC. Of these, 33 trials are in Phase I or Phase I/II, 39 in Phase II, three in Phase II/III and six in Phase III trials. The Phase III trials are focused on antimetabolites such as capecitabine and gemcitabine, and anthracyclines such as epirubicin, with designs focused on either the neoadjuvant or adjuvant chemotherapy setting.

The ongoing Phase I and Phase I/II trials are primarily combination therapies, such as temsirolimus (mTOR kinase inhibitor) + neratinib (dual HER-2, EGFR, tyrosine kinase inhibitor); erlotinib (tyrosine kinase inhibitor, targets EGFR) + metformin (activates AMPK) [69]; dinaciclib (selective cyclin-dependent kinases inhibitor) [70] + epirubicin hydrochloride (anthracycline chemotherapy); Notch signaling pathway inhibitor RO4929097 + paclitaxel and carboplatin; combination of BKM120 (selective PI3K inhibitor) [71–73] and olaparib (PARP inhibitor) [74–76]; veliparib (PARP inhibitor) [77–79] + cisplatin + vinorelbine ditartrate (semisynthetic vinca alkaloid antimitotic chemotherapy) [80,81]; panobinostat (HDAC inhibitor) [82,83] + letrozole [84,85]; PLX 3397 [86] and eribulin; and cediranib (EGFR tyrosine kinase inhibitor) and olaparib [74–76]. Two ongoing early trials incorporate chemotherapy with radiation therapy, including cisplatin plus radiation therapy and concurrent adjuvant carboplatin with accelerated radiotherapy.

Recent FDA guidance in breast cancer

In May of 2012, the FDA released a draft guidance [201] outlining the usage of pCR as the primary outcome for high-risk early-stage neoadjuvant breast cancer clinical trials in order to promote approvals of promising therapies based on accelerated approval regulations (part 314, Code of Federal Regulations, title 21 [H] and title 601 [E]) [87]. The draft guidance provides insight on clinical trial design and statistical considerations and characterization of drug safety, in addition to the rationale for use of pCR as a surrogate end point. Available adjuvant therapies have prolonged breast cancer survival such that trials in that setting could take more than a decade for approval in the metastatic population. Thus, the neoadjuvant setting will have the dual advantage of breast conservation as well as well-determined

outcomes based on pCR. This will benefit the subpopulations of patients with substantial risk of recurrent disease, such as those with TNBC and BLBC. A meta-analysis of 14 trials comparing pre- with post-operative chemotherapy identified 50% less risk of death in patients with pCR when compared with patients with residual tumor [88]. Since TNBC patients are chemosensitive [89–91], it is anticipated that this guidance could lead to accelerated approvals for drugs to benefit this population. According to this draft guidance, randomized add-on (combination) blinded trials will be preferred, with a uniform definition of pCR, and avoidance of postoperative systemic therapy so that continued patient follow-up can more clearly inform the utility of the surrogate end point. The guidance further delineates that an analysis of pCR, disease-free survival and/or overall survival should be prespecified and planned in the protocols for those trials seeking accelerated approval status, and should incorporate the entire intent-to-treat population. The FDA also anticipates that a large difference in pCR will be necessary in order to produce a resulting statistically significant difference in disease-free survival or overall survival, but ‘large’ is not further defined and is the subject of additional research through meta-analysis.

Discussion

While it is encouraging that a great deal of effort has provided appropriate evidence for potential clinical trials for TNBC, recent progress has also demonstrated the need for novel trial design in order to appropriately account for the heterogeneity of TNBC and BLBC and potential targeted therapies. Research efforts should focus on best approaches to adaptive, flexible trial designs in the targeted therapy setting, designs that focus on the incorporation of molecular indicators for therapy selection. The I-SPY2 trial has provided a framework to begin this important direction in the neoadjuvant setting [92]. In addition, based on the epidemiological evidence, multidisciplinary approaches to the inclusion of vulnerable populations (defined by individual and area-level characteristics) in clinical trials will be particularly critical in TNBC [93,94]. The regulatory authorities have demonstrated leadership by providing two draft guidance documents, one focused on appropriate outcomes in at-risk populations for accelerated approval [201], and the other focused on adaptive design trials [95,96]. These trials will require multidisciplinary, multi-institution and multicompany alliances in order to be successful.

Future perspective

We present evidence of the molecular heterogeneity of TNBC and BLBC, diseases that presents clinical challenges of poorer survival outcomes. Epidemiological evidence is also presented that indicates African-American patients and socioeconomically disadvantaged patients are more likely to present with TNBC. Future clinical trials in TNBC will benefit from input from multiple disciplines to inform creative design, multifactorial combination targeted therapies, access to diverse populations and strength in analytics to assure the best outcomes to address the heterogeneity of disease subclassification.

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Executive summary

Molecular heterogeneity of breast cancer

■ Triple-negative breast cancer (TNBC) is primarily diagnosed by the absence of expression of hormone receptors (estrogen receptor, progesterone receptor) and HER-2. While there is overlap with the molecularly defined basal-like breast cancer (BLBC), TNBC exhibits diversity of expression with regard to cytokeratins, EGF receptor, caveolins and other key genes that distinguish and further establish tumor heterogeneity.

Epidemiological evidence of disparities in breast cancer & differential molecular subtype

■ TNBC and BLBC typically occur in younger women, occur more frequently in patients with germline *BRCA1* mutations, and exhibit a number of adverse pathological features including higher stage and grade, with extensive epidemiological evidence of predilection to TNBC and BLBC in African-American and socioeconomically disadvantaged populations. Despite high rates of response to chemotherapy, TNBC and BLBC patients have a higher likelihood of relapse and therefore worse prognosis.

Ongoing clinical trials in TNBC

■ Numerous targeted and combination therapies are currently under study including those regarding PARP-1/2, EGFR and kinase inhibitors. New evidence of the structural basis for PARP-1 and the domain interfaces required for DNA-dependent activity presents potential targets for design of novel PARP-1 inhibitors.

Recent US FDA guidance in breast cancer & discussion

■ Clinical trial designs in TNBC will require multidisciplinary teams to provide insight on design, selective biomarker-target therapy relationships and access to appropriate at-risk populations, along with analytic work-flows to ensure successful clinical trials.

Table 1

Epidemiological evidence of characteristics related to differential outcomes for minority breast cancer patients.

Study (year)	Study design	Study population	Cause of disparity	Outcome	Ref.
Ademuyiwa <i>et al.</i> (2011)	Review	Not applicable	Lifestyle/environment	Grade and receptor status	[20]
Andaya <i>et al.</i> (2012)	Registry	184,602 cases	Lifestyle/environment	Receptor status	[22]
Barrett <i>et al.</i> (2008)	Registry	21,516 cases	Lifestyle/environment	Stage (distant metastasis)	[30]
Campbell <i>et al.</i> (2009)	Registry	25,900 cases	Lifestyle/environment	Stage	[32]
Cho <i>et al.</i> (2011)	Registry	42,714 cases	Lifestyle/environment	Stage	[33]
Clarke <i>et al.</i> (2010)	Registry	33,199 cases	Lifestyle/environment	Receptor status	[46]
Clegg <i>et al.</i> (2009)	Registry	20,149 cases	Lifestyle/environment	Stage	[97]
Cunningham <i>et al.</i> (2010)	Registry	95,159 cases	Lifestyle/environment	Receptor status and grade	[42]
Dai (2010)	Registry	10,087 cases	Lifestyle/environment	Stage	[34]
Desantis <i>et al.</i> (2010)	Registry	193,969 cases	Lifestyle/environment	Receptor status, grade, tumor size, lymph node status and metastasis	[43]
Dolle <i>et al.</i> (2009)	Case-control	897 cases, 1569 controls	Lifestyle/environment	Receptor status	[23]
Dunn <i>et al.</i> (2010)	Review	Not applicable	Lifestyle/environment	Receptor status	[47]
Echeverria <i>et al.</i> (2009)	Registry	4589 cases	Lifestyle/environment	Stage	[35]
Enewold <i>et al.</i> (2012)	Registry	240,040 cases	Lifestyle/environment	Stage	[98]
Gerend and Pai (2008)	Review	Not applicable	Personal health beliefs	Stage	[99]
Gregg (2009)	Review	Not applicable	Personal health beliefs	Stage	[100]
Gullatte <i>et al.</i> (2010)	Retrospective	129 cases	Personal health beliefs	Stage	[101]
Haas <i>et al.</i> (2008)	Registry	86,723 cases	Lifestyle/environment	Stage	[36]
Hahn <i>et al.</i> (2007)	Case-control (case only)	829 cases	Lifestyle/environment	Stage	[31]
Halpern <i>et al.</i> (2007)	Registry	533,715 cases	Lifestyle/environment	Stage	[102]
Harper <i>et al.</i> (2009)	Registry	Not provided	Lifestyle/environment	Stage	[103]
Henry <i>et al.</i> (2011)	Registry	161,619 cases	Lifestyle/environment	Stage	[28]
Kabat <i>et al.</i> (2011)	Prospective	148,030 subjects	Lifestyle/environment Receptor	status	[48]
Keegan <i>et al.</i> (2012)	Registry	112,256 cases	Lifestyle/environment	Receptor status	[49]
Keller <i>et al.</i> (2011)	Registry	1,388,186 cases	Lifestyle/environment	Stage and tumor histology	[37]
Kouri <i>et al.</i> (2010)	Registry	403,325 cases	Lifestyle/environment	Stage	[104]
Krieger <i>et al.</i> (2008)	Registry	42,420 cases	Lifestyle/environment	Receptor status	[51]
Krieger <i>et al.</i> (2011)	Registry	291,569 cases	Lifestyle/environment	Receptor status	[50]
Kuo <i>et al.</i> (2011)	Registry	33,838 cases	Lifestyle/environment	Stage	[29]

Study (year)	Study design	Study population	Cause of disparity	Outcome	Ref.
Kuzmiak <i>et al.</i> (2008)	Registry	617 cases	Lifestyle/environment	Stage and tumor size	[44]
Kwan <i>et al.</i> (2009)	Prospective (case only)	2544 cases	Lifestyle/environment	Receptor status	[52]
Lew <i>et al.</i> (2009)	Prospective	184,418 subjects	Lifestyle/environment	Receptor status	[53]
Li <i>et al.</i> (2010)	Prospective	87,724 subjects	Lifestyle/environment	Receptor status and tumor histology	[54]
Lund <i>et al.</i> (2009)	Case-control (case only)	831 cases	Lifestyle/environment	Receptor status	[26]
Lund <i>et al.</i> (2008)	Registry	190 cases	Lifestyle/environment	Receptor status	[55]
Markossian <i>et al.</i> (2012)	Registry	23,500 cases	Lifestyle/environment	Stage	[38]
Martinez <i>et al.</i> (2007)	Registry	25,494 cases	Lifestyle/environment	Receptor status	[57]
McBride <i>et al.</i> (2007)	Registry	256,174 cases	Lifestyle/environment	Tumor size and positive lymph nodes	[27]
Millikan <i>et al.</i> (2008)	Case-control	1424 cases, 2022 controls	Lifestyle/environment	Receptor status	[58]
Morris and Mitchell (2008)	Review	Not applicable	Lifestyle/environment	Stage and receptor status	[25]
Ooi <i>et al.</i> (2011)	Registry	229,594 cases	Lifestyle/environment	Stage and receptor status	[56]
Parise <i>et al.</i> (2009)	Registry	61,309 cases	Lifestyle/environment	Receptor status	[15]
Parise <i>et al.</i> (2010)	Registry	69,358 cases	Lifestyle/environment	Stage	[64]
Reyes-Ortiz <i>et al.</i> (2008)	Registry	20,818 cases	Lifestyle/environment	Stage	[39]
Schootman <i>et al.</i> (2009)	Registry	35,937 cases	Lifestyle/environment	Distant metastases	[105]
Setiawan <i>et al.</i> (2009)	Prospective	84,427 subjects	Lifestyle/environment	Receptor status	[59]
Stark <i>et al.</i> (2010)	Registry	1664 cases	Lifestyle/environment	Receptor status	[60]
Stead <i>et al.</i> (2009)	Registry	415 cases	Lifestyle/environment	Receptor status	[61]
Tarlov <i>et al.</i> (2009)	Registry	4533 cases	Lifestyle/environment	Stage	[40]
Telli <i>et al.</i> (2011)	Registry	126,577 cases	Lifestyle/environment	Receptor status	[62]
Trivers <i>et al.</i> (2009)	Case only	476 cases	Lifestyle/environment	Receptor status	[63]
Virmig <i>et al.</i> (2009)	Registry	273,265 cases	Lifestyle/environment	Stage	[106]
Vona-Davis and Rose (2009)	Review	Not applicable	Lifestyle/environment	Stage, grade and receptor status	[45]
Ward <i>et al.</i> (2010)	Registry	172,834 cases	Lifestyle/environment	Stage	[107]
Warner and Gomez (2010)	Registry	124,009 cases	Lifestyle/environment	Stage	[41]