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Breast Cancer Characteristics Among World Trade Center-Exposed Survivors

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Abstract

Background: The September 11, 2001, World Trade Center (WTC) disaster exposed local community members to a complex mixture of known and suspected carcinogens, raising concerns about long-term cancer risk. The objective of the current study was to characterize breast cancer among women enrolled in the WTC Environmental Health Center (EHC) and compare findings with population-based data.

Methods: This observational study included civilian survivors enrolled in the WTC EHC through December 31, 2024. Female breast cancer characteristics, including age at diagnosis, stage at presentation, molecular subtype distribution, and occurrence of multiple primary cancers were analyzed. Breast cancer characteristics were compared with data from the Surveillance, Epidemiology, and End Results (SEER-21) Program.

Results: Among 17,449 individuals with certified enrollment in the WTC EHC, 7,274 were diagnosed with cancer, including 1,575 patients with breast cancer (1,553 women and 22 men). The median age at breast cancer diagnosis among women in the WTC EHC was lower than in the SEER-21 data (56.5 vs 60 years). A higher proportion of WTC EHC breast cancers were diagnosed at an early stage (stages 0 and I) than in SEER-21 (70.9% vs 61.6%). The proportion of luminal A tumors was lower in the WTC EHC compared with SEER-21 (49.8% vs 56.9%), a pattern observed across racial and ethnic groups. Approximately one-quarter of women with breast cancer had more than one primary cancer diagnosis. The most frequent second primary cancers were breast, nonmelanoma skin, thyroid, and lung cancers.

Conclusions: Breast cancer among WTC-exposed civilian women demonstrates differences in age at diagnosis, stage distribution, and molecular subtype patterns compared with the general population. These findings highlight the need for continued surveillance and investigation of exposure-related factors influencing breast cancer risk and biology in this population.

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Introduction

The question of an increased cancer risk has been raised in rescue and recovery workers and local community members (local workers, residents, commuters, students) who were exposed to a complex mixture of known and suspected carcinogens after the destruction and collapse of the World Trade Center (WTC) towers and surrounding buildings on September 11, 2001 [1-10]. Breast cancer is the most common cancer among women in the United States, excluding nonmelanoma skin cancer [11]. Although WTC dust and fumes contained multiple agents implicated in breast cancer etiology such as polychlorinated biphenyls, perfluoroalkyl substances, and fire-retardant materials, early studies of breast cancer outcomes among WTC-exposed responder cohorts were hindered by the predominance of men and the small number of breast cancer cases [6,12]. In initial studies using World Trade Center Health Registry data through 2011, Li et al. reported an increased incidence of breast cancer among WTC-exposed female civilians not involved in rescue and recovery (Standardized Incidence Ratio [SIR], 1.34 [95% CI, 1.15–1.55]) and a nonsignificant increase among female rescue and recovery workers (SIR, 1.22 [95% CI, 0.90–1.61]) [8]. No excess was observed among general responder workers enrolled in the WTC Health Programs from 2003 to 2013 (SIR, 0.94 [95% CI, 0.69–1.24]) [10].

Civilian populations exposed to the WTC dust and fumes remain understudied. These groups include local workers, residents, students and those in southern Manhattan on 9/11/2001.

These individuals had potential acute and/or prolonged exposure to WTC dust and fumes, often without adequate respiratory protection [13,14]. These community members (termed survivors) are eligible to enroll in the Centers for Disease Control and Prevention (CDC) and the National Institute for Occupational Safety and Health (NIOSH)-funded WTC Health Program if they fit specific criteria [15]. The Health and Hospitals (H+H) WTC Environmental Health Center (WTC EHC) is a Center of Excellence for survivors in the WTC Health Program and includes ~ 50% women. We previously described the distribution of cancer cases in patients enrolled in the WTC EHC and reported that breast cancer was the most common cancer in these women [16,17]. We characterized 592 female breast cancer cases identified in these women as of 12/31/2019 [18] and described male breast cancer patients in a separate report [19]. Over the past 5 years, the number of breast cancer cases in the WTC EHC program has continued to increase. The main objective of this study is to provide updated demographic and cancer characteristics of female breast cancer patients enrolled in the WTC EHC Program as of 12/31/2024.

Methods

Study participants

World trade center environmental health center (WTC EHC): The WTC EHC is part of the WTC Health Program, established by the CDC-NIOSH. Until recently, the WTC EHC was the only program providing medical and mental health care to local community members (survivors) exposed to the September 11, 2001, World Trade Center (WTC) disaster [20,21]. The WTC EHC remains the largest of the programs serving the survivor population within the WTC Health Program.

Eligibility for enrollment in the WTC Health Program requires documented presence in the New York City disaster area, defined as the area of Manhattan south of Houston Street and any block in Brooklyn wholly or partially within a 1.5 mile radius of the former WTC site, along with at least one of the following exposure criteria: 1) direct exposure to the dust cloud on September 11, 2001; 2) residence, employment, school attendance, child care, or adult day care for at least 30 days between September 11, 2001, and October 1, 2002; or 3) employment as a cleanup or maintenance worker with extensive WTC dust exposure during the same period who did not meet general responder eligibility criteria [15]. In addition, the WTC Health Program requires a defined “certifiable” health condition for entry into the program [15].

The WTC EHC was established through collaborative efforts among the affected community, organized labor, and the medical community [20]. The program was authorized under the James Zadroga 9/11 Health and Compensation Act of 2010 (H.R. 847). Initially, only aerodigestive and mental health conditions were designated as certifiable; cancer was added as a certifiable condition in 2012. Individuals diagnosed with cancer before 2012 were eligible for enrollment if they met the minimum latency requirement for cancer defined by WTC Health Program guidelines. For solid tumors, including breast cancer, the minimum latency period was 4 years between WTC exposure and initial cancer diagnosis [22].

Unlike several responder cohorts, the WTC EHC population is ethnically and racially diverse, with women comprising approximately half of enrollees. Participation is based on self-referral, and enrollment requires documentation of a certifiable WTC-related health condition [21].

Information on lifestyle characteristics, including smoking status, was self-reported via structured questionnaires at enrollment and reflected status as of September 11, 2001. Height and weight were measured at enrollment, and body mass index was calculated accordingly.

Characterization of breast cancer

Breast cancer characteristics were obtained from the WTC EHC Pan-Cancer Database (PCDB), a comprehensive registry developed to capture information on all cancer diagnoses among WTC EHC enrollees and linked to the WTC EHC clinical database [17]. Data capture and management were conducted by using REDCap, a secure environment compliant with the Federal Information Security Modernization Act (FISMA) and the Health Insurance Portability and Accountability Act (HIPAA). The PCDB includes 3 primary domains: patient demographics, site-specific cancer characteristics, and cancer biomarker information [17].

Breast cancer data were abstracted from pathology reports, clinical records, and other available medical documentation. All cancer-related data underwent standardized review by trained medical personnel at the WTC EHC. Recorded variables included age at diagnosis, tumor anatomic site (International Statistical Classification of Diseases, Tenth Revision), tumor size, histologic grade, histology (International Classification of Diseases for Oncology), Tumor-Node-Metastasis (TNM) classification, and disease stage. The analysis included individuals diagnosed with ductal carcinomas (International Classification of Diseases for

Oncology codes 8140, 8500–8505, and 8514), lobular carcinomas (code 8520), and mixed carcinomas (codes 8521–8524).

Breast cancer molecular subtypes were defined using immunohistochemical expression of Hormone Receptors (HR): Estrogen Receptor (*ER*) and Progesterone Receptor (*PR*), as well as Human Epidermal growth factor Receptor 2 (*HER2*), which serve as clinical surrogates for gene expression–based intrinsic subtypes [23-25]. Four molecular subtypes were classified as follows: luminal A (HR-positive and *HER2*-negative), luminal B (HR-positive and *HER2*-positive), triple-negative (HR-negative and *HER2* negative), and *HER2*-enriched (HR-negative and *HER2*-positive).

Second primary tumors, defined according to criteria established by the International Association of Cancer Registries and the International Agency for Research on Cancer, were also recorded. The PCDB includes information on the medical facilities where biopsies and surgical procedures were performed to facilitate future tissue retrieval.

Breast cancer data from the Surveillance, Epidemiology, and End Results (SEER) Program were used for comparison. SEER-21 database provides incidence and survival data from 2000 to 2022 and additionally included hormone receptor status and molecular subtype information for the same period.

Cancer-free WTC-exposed individuals included enrollees with respiratory or digestive or mental health conditions and were drawn from the same source population as breast cancer cases.

For this analysis, we included female patients with a diagnosis of *breast* cancer who were enrolled in the WTC EHC from three sites (Bellevue, Gouverneur and Elmhurst hospitals) as of 31 December 2024 according to the latency rules defined by the WTC Health Program [22].

We also included WTC EHC participants without a certified cancer diagnosis who were enrolled at WTC EHC during the same period as a non-cancer group. All analyses were performed using de-identified data and approved by the New York University School of Medicine Institutional Review Board (IRB# i06-1).

Data analysis

WTC exposure characteristics, demographic variables, and tumor features were summarized using descriptive statistics, including medians and interquartile ranges for continuous variables and counts and percentages for categorical variables. Group differences were assessed using the χ^2 test or Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables. All statistical tests were 2-sided, with a significance threshold of $P < .05$. Analyses were performed using *R* statistical software, version 4.5.0 (*R* Foundation for Statistical Computing).

Results

Demographic and exposure characteristics

As of December 31, 2024, a total of 17,449 individuals were enrolled in the WTC EHC. Among these, 7,274 participants were diagnosed with cancer of any type, including 1,575 persons with a primary breast cancer diagnosis (1,553 women and 22 men).

Breast cancer was the most frequently diagnosed cancer among women in the WTC EHC, accounting for almost half (49.6%) of all female cancer diagnoses. Among the 1,553 women with breast cancer, 101 women had two primary breast cancer diagnoses, yielding a total of 1,654 breast cancer diagnoses (Figure 1).

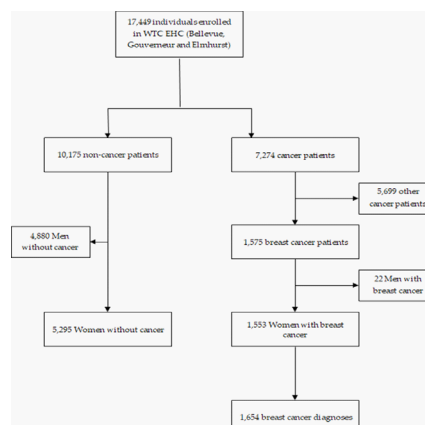


Figure 1: Flow diagram of breast cancer diagnoses in the WTC EHC as of December 31, 2024.

Table 1 summarizes the demographic and exposure characteristics of female breast cancer patients ($n=1,553$) and female WTC EHC participants without cancer ($n=5,295$). The median age at diagnosis of breast cancer was 56.5 years with a median latency of 15 years from 9/11/01. The WTC EHC population was racially and ethnically diverse, comprising approximately 14% Hispanic, 28% non-Hispanic Black, 17% non-Hispanic Asian, and 40% non-Hispanic White women. Women with breast cancer compared to cancer-free female participants included a higher proportion of non-Hispanic White women (39.9 vs 32.1%) and non-Hispanic Asian women (17% vs 13%) and a lower proportion of Hispanic women (14% vs 26%). A higher proportion of women with breast cancer were more likely to have higher household income and education beyond high school than cancer-free participants (Table 1). Patients with breast cancer had a similar BMI to cancer-free women. Most women were never smokers, including 71% of women with breast cancer and 68% of cancer-free women. Among smokers, a higher proportion of women with breast cancer reported >5 pack-years tobacco use (26%) compared to women without breast cancer (22%) (Table 1).

Table 2 presents the median age at breast cancer diagnosis by race and ethnicity in the WTC EHC and SEER data as of 2021. The median latency period ranged from 14 to 15 years across most racial and ethnic groups. The overall median age at diagnosis in the WTC EHC was lower than that reported in the SEER-21 database (56.5 vs 60 years). Compared with SEER-21, the median age at breast cancer diagnosis was lower in the WTC EHC among non-Hispanic White women (57 vs 61 years) and Asian women (55 vs 57 years).

Breast cancer characteristics

Table 3 summarizes tumor characteristics of primary breast cancers diagnosed among women in the WTC EHC and data from the SEER-21 program [26]. Breast cancer diagnoses in the WTC EHC were evenly distributed on the right and left side, a finding that was similar to SEER-21 data. Invasive breast cancer (stage I-IV) accounted for most diagnoses (75.2%).

Invasive ductal carcinoma (85%) and invasive lobular carcinoma (9%) were the most common histological subtypes. A lower proportion of tumors in the WTC EHC cohort were grade 1 (well differentiated) compared with SEER-21 (12.7% vs 18.1%). In addition, compared with SEER-21, WTC EHC breast cancers had a lower proportion of large primary tumors (≥ 5 cm; 2.9% vs 6.3%) and fewer tumors with distant metastases at diagnosis (stage IV; 1.0% vs 4.2%). The proportion of early-stage breast cancer (stages 0 and I) was higher in the WTC EHC cohort than in the SEER-21 database (70.9% vs 61.6%) (Table 3). Although the number of breast cancer diagnoses in the current analysis is much larger, the findings are consistent with the previous report [18].

Breast cancer biomarker characteristics

Hormone receptors (*ER*, *PR*) status was available for 83.7% and *HER2* expression status was available for 71.6% of breast cancer diagnoses. The distribution of breast cancer molecular subtypes overall and by the dust cloud exposure in the WTC EHC is presented in Table 4.

Luminal A (HR-positive, *HER2*-negative) was the most common molecular subtype accounting for about half of all breast cancers in the WTC EHC, followed by luminal unspecified (HR-positive, *HER2* unknown) (12.1%) and luminal B (HR-positive, *HER2*-positive) (8.8%) subtypes. Triple (*ER*, *PR*, *HER2*) negative accounted for 9.3% of breast cancer cases and *HER2*-enriched (HR-negative,

HER2-positive) tumors comprised 3.7% of cases in the WTC EHC. The distribution of molecular subtypes was similar by the dust cloud exposure status in the WTC EHC (Table 4).

Compared with SEER-21 data, breast cancer cases exposed to the WTC dust had a slightly higher proportion of triple-negative (8.3% vs 10.1%, respectively), and a lower proportion of Luminal A tumors (56.9% vs 49.8%, respectively) (Table 4). These findings were similar to our previous report [18].

Because breast cancer molecular subtypes vary by race and ethnicity, Table 5 presents the distribution of molecular subtypes by race and ethnicity in the WTC EHC compared with available SEER data [26,27]. Among non-Hispanic Black women with breast cancer in the WTC EHC, 18% had triple-negative tumors, similar to proportions reported in SEER-21 data. The proportion of triple-negative tumors were similar in the WTC EHC and in SEER-21 data among Hispanic and Asian women (Table 5). Luminal A subtype proportions were consistently lower among all racial/ethnic groups compared with SEER-21 (Table 5).

Twenty-five percent of women with breast cancer enrolled in the WTC EHC (395 of 1,553) had more than one primary cancer diagnosis. The most common second primary solid tumors were nonmelanoma skin cancer (27%), second primary breast cancer (26%), thyroid (7%) and lung cancer (6%), consistent with the prior report [18].

Table 1: Demographic characteristics of female patients in the WTC EHC with and without breast cancers as of December 31, 2024.

Characteristic		Non-cancer n=5,295	Breast cancer n=1,553
Age on 9/11, years median [IQR]		42 [33.00, 49.00]	43 [35.00, 50.00]
Age at diagnosis, years median [IQR]		-	56.5 [49.00, 65.00]
Age group on 9/11, n (%)	<20	313 (5.9%)	8 (0.6%)
	21-29	590 (11.1%)	143 (10.2%)
	30-39	1,389 (26.2%)	385 (27.4%)
	40-49	1,755 (33.1%)	496 (35.3%)
	50-59	972 (18.4%)	322 (22.9%)
	60-69	213 (4.0%)	44 (3.1%)
	70-79	57 (1.1%)	6 (0.4%)
	≥ 80	6 (0.1%)	0 (0.0%)
Race/Ethnicity, n (%)	Non-Hispanic White	1,630 (32.1%)	540 (39.9%)
	Non-Hispanic Black	1,362 (26.8%)	383 (28.3%)
	Hispanic	1,326 (26.1%)	190 (14.0%)
	Non-Hispanic Asian	672 (13.2%)	232 (17.1%)
	Native American/Pacific Islander	15 (0.3%)	3 (0.2%)
	Other	79 (1.6%)	5 (0.4%)
BMI, n (%)	Normal weight (<25)	597 (30.2%)	219 (30.7%)
	Overweight (25 – 30)	598 (30.2%)	244 (34.2%)
	Obese (≥ 30)	784 (39.6%)	250 (35.1%)
Individual income n (%)	$\leq$ \$30,000/year	1,028 (56.6%)	468 (52.1%)
	> \$30,000/year	789 (43.4%)	431 (47.9%)
Education, n (%)	High school or less	1,349 (27.8%)	320 (23.6%)
	More than high school	3,496 (72.2%)	1,035 (76.4%)
Smoking status, n (%)	Never smoker	3,566 (67.8%)	997 (71.4%)
	Former and current smokers	1,690 (32.2%)	400 (28.6%)
Smoking pack-years, n (%)	≤ 5 pack-year	3,582 (77.6%)	1,004 (74.4%)
	>5 pack-year	1,032 (22.4%)	345 (25.6%)

Table 2: Age at breast cancer diagnosis by race and ethnicity in the WTC EHC compared to the SEER-21 data.

Race/Ethnicity	N	Age at diagnosis	
		WTC EHC Median [IQR]	SEER 21 (Hendrick et al, 2021) (46) Median [IQR]
Non-Hispanic White	540	57.00 [50.00, 65.00]	61.00 [53.00, 67.00]
Non-Hispanic Black	383	57.00 [49.00, 65.00]	58.00 [51.00, 66.00]
Hispanic	190	56.00 [49.00, 65.00]	56.00 [49.00, 64.00]
Non-Hispanic Asian	232	55.00 [48.00, 63.00]	57.00 [49.00, 65.00]
Native American/Other	8	64.00 [52.00, 68.00]	59.00 [51.00, 66.00]
Overall	1,353	56.50 [49.00, 65.00]	60.00 [52.00, 67.00]

Table 3: Breast cancer characteristics among female patients in WTC EHC.

Characteristic		WTC EHC n (%)	SEER 21 n (%)
		n=1,553	n=1,671,628
Laterality, n (%)	Left	774 (49.8%)	841,402 (50.3%)
	Right	768 (49.5%)	813,899 (48.7%)
	Bilateral	7 (0.5%)	743 (<0.1%)
	Unknown	4 (0.3%)	15,584 (0.9%)
Stage, AJCC * (%)	0	324 (20.9%)	320,502 (19.2%)
	I	777 (50.0%)	709,390 (42.4%)
	II	316 (20.3%)	370,895 (22.2%)
	III	60 (3.9%)	131,206 (7.8%)
	IV	16 (1.0%)	56,472 (3.4%)
	Unknown	60 (3.9%)	83,163 (5.0%)
Grade, n (%)	G1. Well-differentiated	197 (12.7%)	302,719 (18.1%)
	G2. Moderately differentiated	702 (45.2%)	629,610 (37.7%)
	G3/G4. Poorly differentiated	447 (28.8%)	484,444 (29.0%)
	Unknown	207 (13.3%)	254,855 (15.2%)
Histology, n (%)	Ductal	1,324 (85.3%)	1,098,207 -65.70%
	Lobular	135 (8.7%)	160,800 (9.6%)
	Mixed	41 (2.6%)	114,322 (6.8%)
	Mucinous	8 (0.5%)	27,807 (1.7%)
	Papillary	12 (0.8%)	3,791 (0.2%)
	Unknown	33 (2.1%)	266,701 (16.0%)
pT (Primary tumor), n (%)	Tis	324 (20.9%)	306,821 (18.4%)
	T1	882 (56.8%)	718,641 (43.0%)
	T2	236 (15.2%)	359,682 (21.5%)
	T3-T4	45 (2.9%)	105,005 (6.3%)
	Unknown	66 (4.2%)	181,479 (10.9%)
pN-Regional lymph nodes, n (%)	N0. No regional lymph node metastasis	1,053 (67.8%)	1174692 (70.30%)
	N1. Regional lymph node metastasis	263 (16.9%)	281,178 (16.8%)
	Unknown	237 (15.3%)	215,758 (12.9%)
pM-Distant metastasis, n (%)	M0. No distant metastasis	1,483 (95.5%)	1,556,229 (93.1%)
	M1. Distant metastasis	16 (1.0%)	70,216 (4.2%)
	Unknown	54 (3.5%)	45,183 (2.7%)

Table 4: Molecular classification of breast cancer subtypes among female breast cancer patients in WTC EHC based on acute WTC dust cloud exposure and compared to the SEER 21 data.

Breast cancer subtype	Hormone receptor status	HER2 status	n (%)	WTC dust cloud exposure on 9/11/01		SEER 21
				No	Yes	
Luminal A (HR+/HER2-)	HR+ (ER+ and/or PR+)	HER2-	774 (49.8%)	349 (50.1%)	355 (50.6%)	583,071 (56.9%)
Luminal B (HR+/HER2+)	HR+ (ER+ and/or PR+)	HER2+	136 (8.8%)	61 (8.8%)	56 (8.0%)	81,691 (8.0%)
Luminal, unspecified	HR+ (ER+ and/or PR+)	Unknown	188 (12.1%)	93 (13.4%)	75 (10.7%)	
Triple-negative (HR-/HER2-)	HR- (ER- and PR-)	HER2-	145	63 (9.1%)	71 (10.1%)	85,054 (8.3%)
HER2-enriched (HR-/HER2+)	HR- (ER- and PR-)	HER2+	57 (3.7%)	22 (3.2%)	28 (4.0%)	34,888 (3.4%)
Unknown			253 (16.3%)	108 (15.5%)	117 (16.7%)	239,587 (23.4%)

Table 5: Breast cancer subtypes by race/ethnicity in WTC EHC compared to the SEER-21 data.

Breast Cancer Subtype	Race/Ethnicity							
	NH White		NH Black		NH Asian		Hispanic	
	WTC EHC n (%)	SEER %	WTC EHC n (%)	SEER %	WTC EHC n (%)	SEER %	WTC EHC n (%)	SEER %
Luminal A (HR+/HER2-), n (%)	295 (64%)	77%	160 (51%)	63%	124 (64%)	73%	99 (61%)	70%
Luminal B (HR+/HER2+), n (%)	47 (10%)	10%	39 (13%)	11%	14 (7%)	12%	14 (9%)	12%
Luminal, unspecified, n (%)	61 (13%)	N/A	46 (15%)	N/A	32 (17%)	N/A	22 (13%)	N/A
Triple-negative (HR-/HER2-), n (%)	32 (7%)	9%	55 (18%)	20%	19 (10%)	9%	22 (13%)	12%
HER2-enriched (HR-/Her2+), n (%)	27 (6%)	4%	11 (4%)	6%	4 (2%)	6%	6 (4%)	6%

Discussion

Women comprise approximately half of the WTC EHC population and the cohort is racially and ethnically diverse. The enrollment of patients in the WTC EHC with cancer has increased over the past 5 years; breast cancer remains the most frequently diagnosed cancer among female survivors enrolled in the WTC EHC. We now report on 1,553 breast cancer cases, a 2.6-fold increase since our last report in 2019 [15].

The median age of diagnosis of breast cancer among patients in the WTC EHC was 56.5 years. This age of diagnosis is lower than the median age (60 years) described for the general population in SEER-21, with earlier median ages also observed among non-Hispanic White women (57 vs 61 years) and Asian women (55 vs 57 years). This finding raises the possibility that the WTC exposure contributed to the onset and progression of breast cancer.

We and other research groups have shown that WTC exposed cancer groups have increased hypermethylation in cancer related gene regions compared with non-exposed cases and controls [28-34]. It is known that hypermethylation of tumor suppressor or DNA repair genes can significantly increase cancer risk. Thus, there is possibility that WTC dust exposure elevated risk for breast cancer and contributed to possibly earlier age of onset [1-10].

Additional potential explanations include increased access to screening, heightened awareness of WTC-related health risks, and possible underlying genetic susceptibility.

Compared with cancer-free women enrolled in the WTC EHC, breast cancer patients included a lower proportion of Hispanic women and a higher proportion of non-Hispanic White and Asian

women. These differences may reflect patterns of self-referral to the WTC EHC as well as the established association between socioeconomic status and breast cancer risk [35-40]. Consistent with this possibility, proxy indicators of socioeconomic status, including higher individual income and educational attainment beyond high school, were more common among women with breast cancer than among cancer-free women in the WTC EHC.

Consistent with our prior report [18], the WTC EHC breast cancer patients had a higher proportion of early-stage breast cancer and fewer tumors with distant metastases at diagnosis compared with SEER-21 population. These findings may reflect greater access to screening and earlier detection of breast cancer among WTC EHC patients. However, potential selection and survival biases should also be considered as possible contributors to these observations.

Immunohistochemical expressions of *ER*, *PR*, and *HER2* from pathology reports were used to classify tumors into 4 common molecular subtypes as previously described [41,42]. Hormone receptor positive and *HER2*-negative (luminal A) subtypes are usually less aggressive, more responsive to hormonal therapy and have a better prognosis than HR-negative and/or *HER2*-positive tumors (Luminal B, *HER2*-enriched), and triple-negative subtypes [27,43,44]. A lower proportion of the WTC EHC patients were Luminal A when compared to SEER-21 (49.8 vs 56.9%). This finding was consistent across all racial and ethnic groups. Although based on a smaller number of cases, the findings suggest racial and ethnic differences in the distribution of intrinsic breast cancer subtypes in the WTC EHC that may differ from those reported for SEER-21. The findings could be clinically relevant given the established associations of molecular subtype with prognosis [45].

Approximately one-quarter of women with breast cancer had more than one primary cancer diagnosis. The occurrence of multiple primary cancers may reflect gene-environment interactions in WTC-exposed patients and warrants further investigation.

This study is a description of breast cancers in the WTC EHC and there are several limitations that suggest the need for further studies. As per the Zadroga Act, enrollment in the WTC EHC is based on self-referral and requires a certifiable diagnosis. As such, breast cancer incidence cannot be estimated, and selection bias may have occurred, particularly among patients with limited or inadequate health insurance. The WTC Health Program supports screening of breast, colorectal, cervical and lung cancer. The screening encouraged by the program may promote early detection, which may have contributed to the lower proportion of advanced or metastatic breast cancers observed in the WTC EHC compared with SEER-21. Data on BRCA1/2 mutation status was unavailable for many patients. The lower proportion of late-stage cases may also reflect survivor bias, with patients having more aggressive disease potentially passing away before enrollment to the program. Some subset analyses by race and ethnicity included small numbers of patients, warranting cautious interpretation. In addition, information on several established breast cancer risk factors, including physical activity, menopausal status, and reproductive history, was not available.

Strengths of this study include the inclusion of women of different racial and ethnic groups, in contrast with prior studies that focused primarily on male first responders. This is also among the first studies to report molecular classification of breast cancer using biomarker data in a WTC-exposed population.

Future research should examine the observed racial and ethnic differences in breast cancer molecular subtypes. Studies using tissue samples and evaluating dysregulated functional pathways in WTC-exposed patients, including those with multiple primary cancers, may yield critical insights into WTC exposure-related carcinogenesis. Given the additional evidence of earlier onset of breast cancer among WTC survivors, consistent with prior findings, further study is warranted to formally evaluate whether WTC dust exposure is associated with a shorter latency period for breast and possibly other cancers.

Declarations

Author contributions:

Conceptualization, A.A.A., J.R., Y.S.; methodology, A.A.A.; N.D., Y.A.A., E.P., E.G., Y.S., Y.L., Z.W.; software, N.D., Y.A.A., E.P.; validation, A.A.A.; N.D., Y.A.A., Y.S., J.R.; formal analysis, Y.A.A., E.P., Y.S.; investigation, A.A.A., N.D.; E.G., Y.A.A., E.P.; resources, Y.S., J.R.; data curation, A.A.A., N.D., Y.A.A., E.P.; writing - original draft preparation, A.A.A.; writing - review and editing, N.D., Y.A.A., Y.S., J.R.; visualization, A.A.A., Y.A.A.; supervision, A.A.A., Y.S., J.R.; project administration, A.A.A., N.D., Y.S., J.R.; funding acquisition, A.A.A., Y.S. and J.R. All authors have read and agreed to the published version of the manuscript.

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