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Urinary Phthalate Metabolite Concentrations and Breast Cancer Incidence and Survival following Breast Cancer: The Long Island Breast Cancer Study Project

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Background: Phthalates, known endocrine disruptors, may play a role in breast carcinogenesis. Few studies have examined phthalates in relation to breast cancer (BC), and, to our knowledge, none have considered survival following BC.

Objectives: We examined 11 urinary phthalate metabolites, individually and as molar sum groupings, in association with BC incidence and subsequent survival.

Methods: Our study includes 710 women diagnosed with first primary BC in 1996–1997 and 598 women without BC from Long Island, New York. Within 3 mo of diagnosis, participants provided spot urine samples. Nine phthalate metabolites were measured in all women; two [monocarboxyoctyl phthalate (MCOP) and monocarboxy-isononyl phthalate (MCNP)] were measured in 320 women with and 205 without BC. Women with BC were followed since diagnosis using the National Death Index; during follow-up (median = 17.6 y), we identified 271 deaths (98 BC related). We examined creatinine-corrected metabolite concentrations in association with: BC, using logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) and all-cause/BC-specific mortality, using Cox regression to estimate hazard ratios (HRs) and 95% CIs. We also examined effect modification by body mass index (BMI) and estrogen receptor (ER) status.

Results: The highest (vs. lowest) quintiles of mono(3-carboxypropyl) phthalate (MCPP), monobenzyl phthalate (MBzP), MCNP, and MCOP were associated with BC ORs ranging from 0.71–0.73. The highest (vs. lowest) quintiles of mono(2-ethylhexyl) phthalate (MEHP) and MCOP were associated with BC-specific mortality HRs of 0.54 (95% CI: 0.28, 1.04) and 0.55 (95% CI: 0.23, 1.35), respectively. For BC-specific mortality, interactions were significant between BMI and mono(2-ethyl-5-oxyhexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), with positive associations among women with BMI <25 and inverse associations among women with BMI $\geq$25.0 kg/m^2.

Conclusions: Consistent with laboratory evidence, we observed inverse associations between urinary concentrations of several phthalate metabolites and BC and subsequent survival; however, these results should be interpreted with caution given that biospecimen collection among women with BC occurred after diagnosis, which may be of particular concern for our case–control findings. https://doi.org/10.1289/EHP2083

Introduction

Phthalic acid diesters, commonly known as phthalates, are man-made chemicals used in a variety of industrial applications. High-molecular-weight phthalates (HMWPs), including di(2-ethylhexyl) phthalate (DEHP), are used primarily as plasticizers to increase the flexibility of vinyl plastic, which is used in many consumer products, such as pharmaceuticals, medical devices, and food packaging (Schettler 2006). Low-molecular-weight phthalates (LMWPs), on the other hand, including diethyl phthalate (DEP) and dibutyl phthalate, are used primarily as solvents in personal care products, such as cosmetics and shampoos (Meeker et al. 2009). Because phthalates are not covalently bound to the plastic matrix, they can leach out, resulting in environmental contamination and human exposure (Bosnir et al. 2003; Rudel et al. 2003; Schettler 2006).

In the body, phthalates rapidly hydrolyze to their corresponding phthalate metabolites (Silva et al. 2003). Metabolites are excreted unchanged or can be further metabolized or conjugated to increase water solubility and facilitate their urinary excretion (Silva et al. 2003). Quantification of phthalate metabolites in urine is the most common and reliable method for assessing phthalates exposure in epidemiological studies (Calafat et al. 2015). Several phthalate metabolites are readily detected in the urine of people in the United States (CDC 2017).

Despite their relatively short biological half-lives, which range from hours to days (Koch et al. 2006), phthalates are hypothesized to have a wide range of adverse health effects due to their potential as endocrine-disrupting chemicals, acting as hormone agonists and antagonists (Okamoto et al. 2011) and as possible carcinogens (ATSDR 2002). Phthalate exposure has been associated with reproductive and developmental outcomes in both animals and humans (Meeker et al. 2009) and with hepatic tumors in F344 rats and B6C3F1 mice chronically administered DEHP, with the lowest-observed-effect level of DEHP carcinogenicity in the rat reported at 0.6% of percentage in feed, and the no-observed-effect level reported at 0.1% of percentage in feed (Ito and Nakajima 2008). Population-based studies examining phthalates in relation to breast cancer (BC) incidence, a hormone-dependent cancer and thus potentially sensitive to environmental xenoestrogens (Brody

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and Rudel 2003), are limited. A study of Mexican women found positive associations between urinary concentrations of monoethyl phthalate (MEP) and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) and inverse associations between monobenzyl phthalate (MBzP) and mono(3-carboxypropyl) phthalate (MCPP) and BC risk (López-Carrillo et al. 2010). More recently, a small study among Alaska-Native women reported a positive association between mono(2-ethylhexyl) phthalate (MEHP) urinary concentrations and BC risk (Holmes et al. 2014). To our knowledge, no studies have examined phthalates in relation to survival following BC.

In the study reported here, we examined the urinary concentrations of 11 phthalate metabolites, measured in a subsample of women who participated in a population-based study, in association with BC and subsequent survival. We also considered associations with LMWP and HMWP metabolites and the sum of four DEHP metabolites. In secondary analyses, we examined effect measure modification by body mass index (BMI) (<25.0, $\geq 25.0\,kg/m^2$) and BC subtype as defined by estrogen receptor (ER) status (ER+ and ER−). We hypothesized that higher phthalate metabolite concentrations, in particular those from phthalates which display estrogenic activity *in vitro* or in animal studies [e.g., MEP, metabolite of DEP (Kumar et al. 2014); and MBzP, metabolite of benzyl butyl phthalate (BBP) (Chen et al. 2014; Kang and Lee 2005)], would be positively associated with BC and subsequent BC-specific mortality. By contrast, we hypothesized that metabolites of antiandrogenic phthalates [e.g., mono-isobutyl phthalate (MiBP) and MCPP, metabolites of di-isobutyl phthalate (DiBP) and of several HMWPs (e.g., MCPP)], and the DEHP metabolites MEHP, mono(2-ethyl-5-oxyhexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), MECPP (Borch et al. 2006), and monocarboxyoctyl phthalate (MCOP), metabolite of di-isononyl phthalate (Howdeshell et al. 2008; Lee and Koo 2007), would be inversely associated with BC and subsequent BC-specific mortality.

Methods

This study uses resources from the Long Island Breast Cancer Study Project (LIBCSP), a population-based study initiated as a case–control study and then continued as a follow-up study. Details of the LIBCSP, including the case–control (Gammon et al. 2002) and follow-up (Parada et al. 2016) study designs, have been previously reported. The LIBCSP study protocol was approved by the Institutional Review Boards of all participating institutions, and written informed consent was obtained from participants prior to data collection.

The analysis of blinded specimens by the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

Study Population

Adult women with a first diagnosis with *in situ* or invasive BC during August 1, 1996 and July 31, 1997 were identified using a rapid reporting system established for the LIBCSP. BC diagnoses were confirmed by each patient's physician and by medical record review; ~82% ($n=1{,}508$) of eligible women with BC completed the main questionnaire. Women without BC were residents of the same two Long Island counties who were frequency matched to the expected distribution of women with BC in 5-y age groups in 1996–1997. Women without BC 65 y of age and older were identified by Health Care Finance Administration (HCFA) rosters, and those under 65 y of age were identified by random digit dialing. HCFA selection occurred twice during the 12-mo identification period that coincided with the 12 mo of patient ascertainment. Random digit dialing selection began July 1, 1996 and continued in eight waves over the following 12 mo. Approximately 63% ($n=1{,}556$) of eligible women without BC completed the main questionnaire. Participants of the LIBCSP ranged in age from 20–98 and were predominantly white (93%) and postmenopausal (67%) (Gammon et al. 2002). Due to the high costs of conducting laboratory assays and the varying availability of funding, we selected samples in two batches for quantification of urinary phthalate metabolite concentrations. The first batch analyzed in 2007 and included a random sample of 400 women with BC and 400 women without BC from among those with available urine. The second batch was analyzed in 2010 and included 493 women with BC who had an available tumor specimen and had not been previously selected, and 250 women without BC who were randomly selected whose urine had not previously been analyzed. We excluded from all analyses 235 women with missing creatinine ($n=224$) or with dilute urine (creatinine <10 mg/dL) ($n=10$), and one that could not be analyzed due to insufficient urine volume, resulting in an analytic sample of 710 women with *in situ* disease ($n=112$) or invasive BC ($n=598$) and 598 women without BC in the case–control design and 710 women with BC in the follow-up design.

Data Collection

Women with BC were enrolled into the LIBCSP, on average within 3 mo of diagnosis (25th percentile = 1.2 mo, 75th percentile = 4.0 mo). At the time of enrollment, all participants completed a comprehensive 100-min interviewer-administered questionnaire. At the time of the interview, 93% of women with BC and 83% of women without BC also donated 25 mL spot urine for laboratory analyses. The ancillary case–control study reported here includes 710 women with BC and 598 women without BC for whom urinary concentrations of 11 phthalate metabolites and creatinine were available; the ancillary follow-up is restricted to the 710 women with BC.

For the follow-up, we determined vital status from diagnosis in 1996–1997 until December 31, 2014, using the National Death Index. *International Statistical Classification of Diseases* codes 9/10 174.9 and C-50.9 listed on the death certificate were used to identify BC-related deaths.

Quantification of Urinary Phthalate Metabolite Concentrations

All urine samples were collected from study participants between 1996 and 1997. Donated urine samples were immediately placed in a cooler with an ice pack and shipped overnight to Columbia University where the samples were processed and stored. The samples were aliquoted and frozen at −80°C within 24 h of collection. Samples selected for urinary biomarker analysis were subsequently shipped overnight on dry ice to the National Center for Environmental Health at the CDC. These shipments occurred in 2007 and 2010. Upon arrival at the CDC, the samples were processed, aliquoted, and stored at or below −20°C until analysis to measure concentrations of creatinine and, using online solid-phase extraction followed by high-performance liquid chromatography-electrospray ionization–isotope-dilution tandem mass spectrometry, of nine phthalate metabolites in both batches: MEP, mono-*N*-butyl phthalate (MnBP), MiBP, MCPP, MBzP, MEHP, MEOHP, MEHHP, and MECPP; and three additional metabolites in the second batch: MCOP, monocarboxy-isononyl phthalate (MCNP), and cyclohexane-1,2-dicarboxylic acid mono(hydroxy-isononyl) ester (MHINCH). This resulted in missing MCOP and MCNP data for 390 women with BC and 393 women without BC. MHINCH, the

Table 1. Distribution of study participant characteristics among the Long Island Breast Cancer Study Project (LIBCSP) women with available values of urinary concentrations of phthalate metabolites and the full sample.

Characteristic	Women with breast cancer		Women without breast cancer	
	Phthalates sample ($n = 710$)	Full sample ($n = 1,508$)	Phthalates sample ($n = 598$)	Full sample ($n = 1,556$)
Age at reference (y)				
<50	195 (27.5%)	407 (27.0%)	197 (32.9%)	499 (32.1%)
50–64	259 (36.5%)	582 (38.6%)	250 (41.8%)	617 (39.7%)
≥65	256 (36.1%)	519 (34.4%)	151 (25.3%)	440 (28.3%)
Income				
<$24,999	154 (21.7%)	286 (19.0%)	104 (17.4%)	295 (19.0%)
$25,000–$49,999	227 (32.1%)	488 (32.4%)	172 (28.8%)	475 (30.6%)
≥$50,000	327 (46.2%)	730 (48.5%)	321 (53.8%)	784 (50.5%)
Missing	2	4	1	2
Education				
<HS/HS graduate	340 (48.0%)	721 (48.0%)	240 (40.2%)	676 (43.6%)
College	261 (36.8%)	551 (36.7%)	263 (44.1%)	651 (41.9%)
Postcollege	108 (15.2%)	230 (15.3%)	94 (15.7%)	225 (14.5%)
Missing	1	6	1	4
Menopausal status				
Premenopausal	225 (32.5%)	472 (31.9%)	211 (37.2%)	503 (33.7%)
Postmenopausal	468 (67.5%)	1,006 (68.1%)	357 (62.8%)	990 (66.3%)
Missing	17	30	30	63
HRT use				
Never	505 (71.2%)	1,096 (72.9%)	439 (73.4%)	1,159 (74.5%)
Ever	204 (28.8%)	408 (27.1%)	159 (26.6%)	396 (25.5%)
Missing	1	4	0	1
Age at menarche (years)				
≤12	310 (44.0%)	658 (44.0%)	274 (46.1%)	677 (43.8%)
>12	394 (56.0%)	837 (56.0%)	321 (53.9%)	870 (56.2%)
Missing	6	13	3	9
Oral contraceptive use				
Never	406 (57.3%)	848 (56.3%)	304 (50.8%)	840 (54.0%)
Ever	303 (42.7%)	657 (43.7%)	294 (49.2%)	715 (46.0%)
Missing	1	3	0	1
Parity/lactation history				
Nulliparous	91 (12.8%)	198 (13.1%)	70 (11.7%)	171 (11.0%)
Parous/never lactated	375 (52.8%)	830 (55.0%)	302 (50.5%)	832 (53.5%)
Parous/ever lactated	244 (34.4%)	480 (31.8%)	226 (37.8%)	553 (35.5%)
Age at first birth (y)				
<20	61 (9.9%)	122 (9.3%)	47 (8.9%)	142 (10.3%)
20–30	450 (72.8%)	969 (74.0%)	421 (79.7%)	1,063 (76.8%)
≥30	107 (17.3%)	218 (16.7%)	60 (11.4%)	180 (13.0%)
Missing	92	199	70	171
Family history of breast cancer				
None	563 (82.1%)	1,166 (79.8%)	498 (84.7%)	1,321 (87.0%)
First degree	123 (17.9%)	295 (20.2%)	90 (15.3%)	197 (13.0%)
Missing	24	47	10	38
BMI at reference (kg/m^2)				
<25.0	315 (44.5%)	683 (45.8%)	309 (52.2%)	750 (49.1%)
25.0–29.9	220 (31.1%)	476 (31.9%)	160 (27.0%)	455 (29.8%)
≥30.0	173 (24.4%)	332 (22.3%)	123 (20.8%)	323 (21.1%)
Missing	2	17	6	28
BMI at age 20 (kg/m^2)				
<25.0	652 (93.0%)	1,377 (93.0%)	534 (90.2%)	1,397 (91.2%)
≥25.0	49 (7.0%)	103 (7.0%)	58 (9.8%)	135 (8.8%)
Missing	9	28	6	24
Alcohol intake				
Never	256 (36.1%)	588 (39.0%)	220 (36.8%)	593 (38.1%)
Ever	454 (63.9%)	920 (61.0%)	378 (63.2%)	963 (61.9%)
Stage				
In situ	112 (15.8%)	235 (15.6%)	—	—
Invasive	598 (84.2%)	1,273 (84.4%)	—	—
Nodal involvement				
No	85 (22.0%)	213 (25.5%)	—	—
Yes	302 (78.0%)	622 (74.5%)	—	—
Missing	323	673	—	—
Tumor size				
≤2 cm	278 (73.5%)	622 (75.5%)	—	—
>2 cm	100 (26.5%)	202 (24.5%)	—	—
Missing	332	684	—	—

Note: LIBCSP women without breast cancer were age-matched to women diagnosed with breast cancer between 1 August 1996 and 31 July 1997. —, no information was collected at that particular examination point; BMI, body mass index; ER, estrogen receptor; HRT, hormone replacement therapy; HS, high school.

Table 1. (*Continued.*)

Characteristic	Women with breast cancer		Women without breast cancer	
	Phthalates sample ($n = 710$)	Full sample ($n = 1,508$)	Phthalates sample ($n = 598$)	Full sample ($n = 1,556$)
ER status				
ER −	115 (23.9%)	264 (26.7%)	—	—
ER +	367 (76.1%)	726 (73.3%)	—	
Missing	228	518	—	
Radiation therapy				
No	191 (38.3%)	401 (39.1%)	—	—
Yes	308 (61.7%)	625 (60.9%)		
Missing	211	482	—	—
Chemotherapy				
No	297 (59.8%)	599 (58.6%)	—	—
Yes	200 (40.2%)	423 (41.4%)	—	—
Missing	213	486	—	—
Hormone therapy				
No	188 (38.1%)	393 (38.9%)	—	—
Yes	305 (61.9%)	616 (61.1%)	—	—
Missing	217	499	—	—

primary metabolite of the nonphthalate plasticizer 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH), was not detected in any samples and, as a result, was not considered further. That MHINCH was undetectable was not surprising given that LIBCSP samples were collected prior to the commercial introduction of DINCH in the United States in 2002 (BASF 2015). Limits of detection (LODs) ranged from $0.2 - 0.6$ μg/L. The laboratory was blinded to any information about the study participants, and in addition to the internal CDC quality control procedures, we incorporated masked quality control specimens (3% and 2% in batches 1 and 2, respectively; total $n = 34$) from a single urine pool in all analysis batches. The coefficients of variation [standard deviation (SD)/mean concentration] for the individual analytes were similar across batches, ranging between 2.5% and 7.2% (median = 4.8%). Ten metabolites were detected among 90% of all women, while one, MEHP, was detected in 78% of women (Table S1). Values below the LOD were imputed as the LOD divided by the square root of 2 (Hornung and Reed 1990). To correct for urine dilution, concentrations (μg/L) were divided by creatinine for final units of micrograms per gram (μg/g) creatinine.

Covariates

As potential confounders, we selected covariates associated with BC incidence or survival as determined from the literature (McPherson et al. 2000; Soerjomataram et al. 2008). Covariates included demographic characteristics [age (continuous), income (<$24,999, $25,000–$49,999, ≥$50,000), education (<high school/high school graduate, college, postcollege)], reproductive factors [menopausal status (pre- or postmenopausal, derived from data on last menstrual period, oophorectomies/hysterectomies, and other surgical information); pregnancy status; lactation status; hormone replacement therapy (HRT) use (Gammon et al. 2002); age at menarche (≤12 or >12 y); parity and lactation history (nulliparous, parous/never lactated, parous/ever lactated); age at first birth (<20, 20–30, ≥30 y)]; family history of BC (none or at least one first-degree relative), exogenous hormone use [oral contraceptive use (never or ever), hormone replacement therapy use (never or ever)]; and lifestyle/behavioral factors [BMI at reference and at age 20 (<25.0, 25.0–29.9, ≥30.0 kg/m^2), alcohol intake (never or ever consuming beer/wine/liquor at least once a month for 6 mo or longer)]. ER status was determined by medical record review.

Statistical Analysis

We categorized creatinine-corrected concentrations into quintiles based on the distributions in the women without BC (Table S2). The correlation between phthalate metabolite concentrations and known BC risk and prognostic factors is uncertain. Thus, we first examined among women without BC Pearson correlations (r_P) between creatinine-corrected urinary phthalate metabolite concentrations and continuous covariates and chi-square tests between quintiles of creatinine-corrected urinary phthalate metabolite concentrations and categorical covariates. Covariates statistically significantly associated with phthalate metabolite concentrations ($p < 0.05$) were selected as potential confounders of the associations between metabolite concentrations and BC incidence and survival. Furthermore, using generalized linear models, among women with BC, we regressed each of the phthalate metabolites on age and chemotherapy treatment prior to urine sample collection to determine the potential effects of chemotherapy on phthalate metabolite concentrations. We also examined age-adjusted phthalate metabolite concentrations by disease and treatment characteristics using generalized linear models regressing each of the phthalate metabolites on each covariate and age to determine whether phthalate metabolite concentrations were associated with more aggressive disease.

We combined metabolites into molar sums that represent similar sources and similar biological activity, LMWP metabolites [ΣLMWPs, the creatinine-corrected molar sum of MEP, MnBP, and MiBP (expressed as MEP, molecular weight 194)], HMWP metabolites [ΣHMWPs, the creatinine-corrected molar sum of MBzP, MEHP, MEOHP, MEHHP, MECPP, excluding MCOP and MCNP (expressed as MEHP, molecular weight 278)], and the sum of four DEHP metabolites [ΣDEHP, the creatinine-corrected molar sum of DEHP metabolites: MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278)] (Teitelbaum et al. 2012).

Case–control analyses. For the primary case–control analyses, we used multivariable unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between quintiles of creatinine-corrected concentrations of the 11 phthalate metabolites, individually and as groupings, and BC. All models included age, and in multivariable models, we additionally adjusted for any known BC risk factors that were statistically significantly correlated ($p < 0.05$) with any of the phthalate metabolites. We also examined log-linear trends using ln-transformed creatinine-corrected metabolite concentrations. In secondary analyses, using tertiles of phthalate metabolite concentrations, we examined effect measure modification by BMI (<25.0 kg/m^2 vs. ≥25.0 kg/m^2) by stratifying the logistic regression models and by including continuous BMI by continuous ln-transformed creatinine-corrected phthalate metabolite

Table 2. Associations between urinary phthalate metabolite concentrations (μg/g creatinine) and risk of incident breast cancer among Long Island Breast Cancer Study Project (LIBCSP) women ($n = 710$ women with breast cancer (BC) and 598 women without breast cancer (no BC).

Analyte (μg/g creatinine)[b]	Median in women with no BC	Age adjusted		Multivariable adjusted[a]	
		BC/no BC	OR (95% CI)	BC/no BC	OR (95% CI)
Total observations	—	710/598	—	682/558	—
MEP					
11.3–60.7	40.2	174/119	1.00	166/115	1.00
60.7–118	87.0	143/120	0.78 (0.56, 1.10)	135/112	0.79 (0.57, 1.12)
118–207	158	120/120	0.67 (0.47, 0.95)	118/109	0.73 (0.51, 1.04)
207–492	314	132/120	0.75 (0.53, 1.05)	126/115	0.75 (0.53, 1.07)
492–34,127	958	141/119	0.81 (0.58, 1.14)	137/107	0.89 (0.62, 1.26)
Ln(MEP)	—	—	0.92 (0.85, 1.00)	—	0.94 (0.86, 1.02)
MnBP					
0.658–19.3	14.0	170/119	1.00	166/112	1.00
19.3–29.0	24.1	125/120	0.70 (0.50, 0.99)	123/113	0.70 (0.49, 1.00)
29.1–43.6	34.1	155/120	0.86 (0.61, 1.20)	148/112	0.85 (0.60, 1.20)
43.9–67.9	52.3	117/120	0.65 (0.46, 0.93)	110/110	0.65 (0.45, 0.93)
67.9–586	104	143/119	0.82 (0.59, 1.16)	135/111	0.79 (0.56, 1.13)
Ln(MnBP)	—	—	0.91 (0.80, 1.04)	—	0.91 (0.79, 1.04)
MiBP					
0.218–1.44	0.938	173/119	1.00	167/112	1.00
1.44–2.43	1.95	140/120	0.81 (0.57, 1.13)	138/112	0.86 (0.60, 1.21)
2.43–3.79	2.97	140/120	0.81 (0.58, 1.14)	132/109	0.80 (0.56, 1.15)
3.79–6.16	4.96	124/120	0.71 (0.51, 1.01)	119/116	0.69 (0.48, 0.99)
6.19–73.3	8.84	133/119	0.78 (0.55, 1.09)	126/109	0.79 (0.55, 1.13)
Ln(MiBP)	—	—	0.90 (0.80, 1.01)	—	0.89 (0.79, 1.00)
MCPP					
0.487–3.27	2.52	173/119	1.00	167/114	1.00
3.28–4.52	3.74	132/120	0.73 (0.52, 1.03)	130/112	0.76 (0.54, 1.08)
4.53–6.45	5.32	159/120	0.85 (0.61, 1.19)	153/113	0.86 (0.61, 1.21)
6.46–9.28	7.51	117/120	0.63 (0.45, 0.90)	109/108	0.64 (0.45, 0.92)
9.31–98.9	14.6	129/119	0.70 (0.50, 0.99)	123/111	0.71 (0.49, 1.01)
Ln(MCPP)	—	—	0.86 (0.74, 1.01)	—	0.85 (0.72, 1.00)
MBzP					
0.411–6.99	4.42	183/119	1.00	177/110	1.00
7.03–10.9	9.08	121/120	0.67 (0.47, 0.94)	119/115	0.64 (0.45, 0.91)
11.0–16.5	13.5	159/120	0.88 (0.63, 1.23)	150/113	0.81 (0.57, 1.14)
16.6–25.7	20.1	113/120	0.63 (0.44, 0.89)	108/112	0.59 (0.41, 0.84)
25.8–505	35.8	134/119	0.74 (0.53, 1.04)	128/108	0.72 (0.50, 1.03)
Ln(MBzP)	—	—	0.94 (0.83, 1.06)	—	0.93 (0.82, 1.05)
MCOP[c]					
0.850–3.40	2.51	78/41	1.00	76/35	1.00
3.45–4.98	4.24	60/41	0.78 (0.45, 1.35)	58/40	0.69 (0.39, 1.24)
5.08–7.42	6.07	60/41	0.74 (0.42, 1.28)	57/37	0.65 (0.36, 1.17)
7.66–13.44	9.81	56/41	0.66 (0.38, 1.16)	53/39	0.54 (0.30, 0.97)
13.69–474	24.4	66/41	0.84 (0.48, 1.45)	64/40	0.73 (0.71, 1.30)
Ln(MCOP)	—	—	0.95 (0.80, 1.12)	—	0.90 (0.75, 1.08)
MCNP[c]					
0.167–1.98	1.51	73/41	1.00	72/37	1.00
2.00–2.64	2.32	39/41	0.51 (0.28, 0.92)	39/41	0.46 (0.25, 0.85)
2.64–3.88	3.17	64/41	0.89 (0.51, 1.55)	61/37	0.85 (0.47, 1.52)
3.96–7.60	5.28	86/41	1.15 (0.67, 1.96)	81/37	1.03 (0.59, 1.82)
7.84–580	13.5	58/41	0.77 (0.44, 1.35)	55/39	0.72 (0.40, 1.30)
Ln(MCNP)	—	—	0.96 (0.79, 1.17)	—	0.95 (0.77, 1.16)
MEHP					
0.238–1.79	1.32	165/119	1.00	160/114	1.00
1.81–3.10	2.41	138/120	0.85 (0.61, 1.20)	132/111	0.85 (0.60, 1.21)
3.13–4.96	4.11	137/120	0.86 (0.62, 1.23)	131/113	0.82 (0.57, 1.17)
4.96–9.86	6.41	146/120	0.94 (0.67, 1.32)	142/112	0.95 (0.67, 1.35)
9.90–1,018	17.0	124/119	0.81 (0.57, 1.15)	117/108	0.79 (0.55, 1.13)
Ln(MEHP)	—	—	0.92 (0.83, 1.02)	—	0.91 (0.82, 1.02)

Note: LIBCSP women without BC were age-matched to women diagnosed with BC between 1 August 1996 and 31 July 1997. —, no information was collected at that particular examination point; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; MBzP, monobenzyl phthalate; MCNP, monocarboxy-isononyl phthalate; MCOP, monocarboxyoctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*N*-butyl phthalate; MWP, molecular-weight phthalate; OR, unconditional logistic regression odds ratio.

[a]Adjusted for age (continuous), age at menarche (continuous), education ($<$ high school/high school graduate, college, and postcollege), menopausal status (pre- vs. postmenopausal), hormone replacement therapy use (never vs. ever), body mass index (<25.0, 25.0–29.9, and $\geq 30.0\,\mathrm{kg/m^2}$), and oral contraceptive use (never vs. ever).

[b]Quintiles (μg/g creatinine) based on distributions among women without breast cancer.

[c]MCOP and MCNP were measured in 320 women with BC and 205 women without BC only.

[d]Low MWP: Creatinine-corrected molar sum of MEP, MnBP, and MiBP (expressed as MEP, molecular weight 194).

[e]High MWP: Creatinine-corrected molar sum of MBzP, MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

[f]ΣDEHP: Creatinine-corrected molar sum of DEHP metabolites: MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

Table 2. (*Continued.*)

Analyte (μg/g creatinine)[b]	Median in women with no BC	Age adjusted		Multivariable adjusted[a]	
		BC/no BC	OR (95% CI)	BC/no BC	OR (95% CI)
MEOHP					
0.882–9.15	6.21	144/119	1.00	141/111	1.00
9.17–14.4	12.2	158/120	1.06 (0.75, 1.49)	150/112	1.01 (0.71, 1.44)
14.5–20.0	16.8	123/120	0.83 (0.58, 1.18)	118/114	0.78 (0.54, 1.12)
20.1–34.0	24.7	149/120	0.97 (0.69, 1.37)	143/111	0.94 (0.65, 1.34)
34.2–1,253	53.5	136/119	0.94 (0.66, 1.33)	130/110	0.89 (0.62, 1.27)
Ln(MEOHP)	—	—	0.96 (0.85, 1.08)	—	0.94 (0.83, 1.06)
MEHHP					
1.10–14.9	9.98	147/119	1.00	143/111	1.00
14.9–23.6	19.8	147/120	0.97 (0.69, 1.37)	140/111	0.93 (0.65, 1.34)
23.8–34.2	28.4	134/120	0.88 (0.62, 1.25)	131/115	0.86 (0.60, 1.24)
34.5–59.4	42.1	140/120	0.89 (0.63, 1.26)	134/112	0.85 (0.59, 1.21)
59.8–2,721	92.7	142/119	0.97 (0.69, 1.37)	134/109	0.92 (0.64, 1.32)
Ln(MEHHP)	—	—	0.99 (0.88, 1.11)	—	0.97 (0.86, 1.10)
MECPP					
3.09–22.3	15.4	152/119	1.00	146/110	1.00
22.5–33.9	28.2	173/120	1.08 (0.77, 1.52)	168/111	1.08 (0.76, 1.53)
34.0–45.9	38.6	112/120	0.70 (0.49, 1.00)	109/114	0.68 (0.47, 0.99)
46.0–78.4	55.8	139/120	0.85 (0.60, 1.20)	134/111	0.82 (0.57, 1.17)
78.9–1,950	131	134/119	0.85 (0.60, 1.20)	125/112	0.79 (0.55, 1.14)
Ln(MECPP)	—	—	0.92 (0.81, 1.04)	—	0.89 (0.78, 1.01)
Low MWP[d]					
24.5–96.4	67.8	163/119	1.00	157/113	1.00
96.4–166	134	174/120	1.04 (0.74, 1.45)	167/112	1.05 (0.74, 1.48)
166–274	216	103/120	0.62 (0.43, 0.88)	98/111	0.63 (0.44, 0.91)
274–527	380	126/120	0.77 (0.55, 1.09)	121/115	0.77 (0.54, 1.10)
530–34,163	1,053	144/119	0.89 (0.63, 1.25)	139/107	0.95 (0.66, 1.35)
Ln(Low MWP)	—	—	0.92 (0.83, 1.01)	—	0.92 (0.84, 1.02)
High MWP[e]					
7.36–60.9	42.3	152/119	1.00	147/110	1.00
61.2–91.4	75.5	161/120	1.05 (0.75, 1.48)	156/116	0.99 (0.69, 1.40)
91.9–122	104	118/120	0.76 (0.53, 1.08)	116/112	0.74 (0.51, 1.06)
123–192	150	133/120	0.83 (0.59, 1.17)	123/110	0.75 (0.52, 1.08)
193–6,320	315	146/119	0.96 (0.68, 1.36)	140/110	0.92 (0.64, 1.32)
Ln(High MWP)	—	—	0.95 (0.83, 1.08)	—	0.92 (0.81, 1.06)
ΣDEHP[f]					
5.45–46.9	33.4	145/119	1.00	141/109	1.00
46.9–71.6	59.4	168/120	1.11 (0.79, 1.55)	162/113	1.05 (0.74, 1.49)
71.7–99.0	83.9	115/120	0.77 (0.54, 1.10)	111/114	0.71 (0.49, 1.02)
99.0–169	123	146/120	0.94 (0.67, 1.33)	137/111	0.87 (0.61, 1.25)
169–6,265	283	136/119	0.92 (0.65, 1.30)	131/111	0.86 (0.60, 1.24)
Ln(ΣDEHP)	—	—	0.94 (0.83, 1.07)	—	0.92 (0.81, 1.05)

concentration interactions in the regression models. In secondary analyses, we also examined phthalate metabolite concentrations in association with BC subtype (ER+ vs. ER− vs. women without BC) using polytomous logistic regression.

Follow-up analyses. For the follow-up analyses, we used Kaplan-Meier survival curves and log[-log(survival)] plots for visual examination of the unadjusted associations with mortality and to assess the proportional hazards assumption (data not shown). We also assessed the proportional hazards assumption using Schoenfeld residuals examining the correlations of the residuals for each exposure with time, log-time, and time^2 as outlined by Allison (Allison 2010). There were no violations of the proportional hazards assumption. In the primary analyses, we used multivariable Cox regression to estimate hazard ratios (HRs) and 95% CIs for all-cause and BC-specific mortality up to 18 y postdiagnosis as related to quintiles of creatinine-corrected phthalate metabolite concentrations. For analyses of all-cause mortality, observations were censored at the end of follow-up, if alive. For analyses using BC-specific mortality as the outcome, non-BC deaths were censored at the time of death. In secondary analyses, we used Cox regression to estimate HRs and 95% CIs for BC-specific mortality within 5 y of BC diagnosis using tertiles of creatinine-corrected phthalate metabolite concentrations. All models included age, and in multivariable models, we additionally adjusted for any covariates that were correlated with any of the phthalate metabolites. We *a priori* hypothesized that estrogen/progesterone status may mediate the association between phthalate metabolite concentrations and BC survival through ER-dependent pathways (Kang and Lee 2005), and thus, in the primary analyses, we did not adjust for ER status or treatment, a potential intermediate (Hammond et al. 2010). In secondary analyses, however, we examined effect measure modification by ER status and BMI by stratifying the Cox regression models by ER status (ER+ vs. ER−) and BMI (<25.0 vs. ≥25.0 kg/m^2), respectively, and by including continuous BMI and dichotomized ER status by continuous phthalate metabolite concentration interactions in the regression models. We examined effect measure modification by ER status for all metabolites except MCOP and MCNP due to small numbers.

All statistical analyses are based on participants with complete data, and participants with missing data were excluded, using SAS (version 9.4; SAS Institute Inc.).

Results

The distributions of study participant characteristics in the subsample for this ancillary study and in the full sample of women with and without BC from the LIBCSP are presented in Table 1.

Table 3. Associations between urinary phthalate metabolite concentrations (μg/g creatinine) and risk of incident breast cancer among Long Island Breast Cancer Study Project (LIBCSP) women with and without breast cancer (BC and no BC), stratified by body mass index (BMI) and for odds of estrogen receptor (ER) + and ER − breast cancer from polytomous logistic regression models.

	Body mass index (BMI) [OR (95% CI)][b]			ER status [OR (95% CI)][b]	
Analyte[a]	<25.0 kg/m² (*n* = 306 BC vs. no BC = 293)	≥25.0 kg/m² (*n* = 376 BC vs. no BC = 265)	$P_{Interaction}$[c]	ER + (*n* = 354 BC vs. no BC = 558)	ER − (*n* = 109 BC vs. no BC = 558)
MEP					
11.3-98.1	1.00	1.00	—	1.00	1.00
98.4–280	0.82 (0.55, 1.21)	0.77 (0.52, 1.16)	—	0.75 (0.53, 1.04)	0.57 (0.34, 0.97)
282–34,127	1.00 (0.67, 1.50)	0.76 (0.52, 1.12)	—	0.80 (0.58, 1.12)	0.87 (0.54, 1.40)
Ln(MEP)	0.98 (0.86, 1.10)	0.90 (0.79, 1.01)	0.25	0.91 (0.81, 1.01)	0.95 (0.81, 1.11)
MnBP					
0.658–25.6	1.00	1.00	—	1.00	1.00
25.7–49.3	0.86 (0.58, 1.28)	0.87 (0.58, 1.28)	—	0.91 (0.65, 1.27)	0.80 (0.49, 1.33)
49.7–586	0.97 (0.66, 1.44)	0.78 (0.52, 1.16)	—	0.97 (0.69, 1.35)	0.79 (0.48, 1.31)
Ln(MnBP)	0.94 (0.78, 1.13)	0.88 (0.72, 1.08)	0.80	0.93 (0.79, 1.10)	0.92 (0.71, 1.17)
MiBP					
0.218–2.07	1.00	1.00	—	1.00	1.00
2.08–4.39	1.02 (0.69, 1.52)	0.73 (0.49, 1.09)	—	0.92 (0.66, 1.29)	0.69 (0.42, 1.14)
4.40–73.3	0.83 (0.56, 1.23)	0.69 (0.46, 1.03)	—	0.88 (0.63, 1.24)	0.62 (0.37, 1.03)
Ln(MiBP)	0.93 (0.79, 1.11)	0.86 (0.72, 1.02)	0.93	0.94 (0.82, 1.09)	0.78 (0.63, 0.97)
MCPP					
0.487–3.98	1.00	1.00	—	1.00	1.00
3.98–7.15	0.96 (0.65, 1.41)	1.17 (0.79, 1.73)	—	0.99 (0.71, 1.38)	1.19 (0.72, 1.97)
7.18–98.9	0.82 (0.55, 1.24)	0.75 (0.50, 1.13)	—	0.76 (0.54, 1.07)	0.98 (0.58, 1.65)
Ln(MCPP)	0.89 (0.71, 1.12)	0.83 (0.65, 1.05)	0.80	0.82 (0.67, 1.00)	0.97 (0.73, 1.30)
MBzP					
0.411–9.70	1.00	1.00	—	1.00	1.00
9.72–18.7	0.67 (0.45, 0.98)	1.12 (0.75, 1.67)	—	0.81 (0.58, 1.13)	1.28 (0.78, 2.10)
18.8–505	0.69 (0.46, 1.03)	0.86 (0.58, 1.28)	—	0.79 (0.56, 1.10)	0.91 (0.53, 1.54)
Ln(MBzP)	0.83 (0.69, 0.99)	1.07 (0.89, 1.28)	0.44	0.96 (0.83, 1.13)	0.95 (0.75, 1.20)
MCOP[d]					
0.850–4.37	1.00	1.00	—	1.00	1.00
4.38–9.09	0.65 (0.34, 1.23)	0.71 (0.37, 1.38)	—	0.58 (0.34, 0.99)	0.49 (0.23, 1.03)
9.18–474	0.64 (0.35, 1.17)	0.68 (0.33, 1.38)	—	0.71 (0.42, 1.19)	0.53 (0.25, 1.11)
Ln(MCOP)	0.93 (0.72, 1.20)	0.85 (0.65, 1.10)	0.53	0.92 (0.74, 1.14)	0.80 (0.58, 1.10)
MCNP[d]					
0.167–2.43	1.00	1.00	—	1.00	1.00
2.45–4.79	1.07 (0.57, 2.00)	0.92 (0.46, 1.83)	—	1.13 (0.67, 1.91)	0.76 (0.34, 1.72)
4.86–580	0.36 (0.73, 2.53)	0.83 (0.42, 1.64)	—	1.04 (0.61, 1.77)	1.49 (0.73, 3.06)
Ln(MCNP)	1.07 (0.81, 1.40)	0.82 (0.60, 1.12)	0.85	0.87 (0.68, 1.11)	0.98 (0.70, 1.37)
MEHP					
0.238–2.62	1.00	1.00	—	1.00	1.00
2.64–5.89	1.01 (0.68, 1.49)	0.76 (0.50, 1.14)	—	0.96 (0.69, 1.35)	0.77 (0.46, 1.29)
5.92–1,018	1.08 (0.73, 1.62)	0.77 (0.52, 1.14)	—	0.98 (0.70, 1.37)	0.97 (0.59, 1.60)
Ln(MEHP)	0.95 (0.81, 1.12)	0.87 (0.76, 1.03)	0.56	0.95 (0.83, 1.08)	0.93 (0.75, 1.13)
MEOHP					
0.882–13.1	1.00	1.00	—	1.00	1.00
13.1–23.3	0.69 (0.47, 1.01)	0.86 (0.57, 1.29)	—	0.88 (0.69, 1.24)	0.72 (0.43, 1.20)
23.4–1,253	0.83 (0.55, 1.24)	0.88 (0.60, 1.29)	—	0.97 (0.69, 1.35)	0.87 (0.53, 1.43)
Ln(MEOHP)	0.99 (0.83, 1.18)	0.90 (0.76, 1.08)	0.94	0.97 (0.83, 1.13)	0.99 (0.79, 1.25)
MEHHP					
1.10–21.3	1.00	1.00	—	1.00	1.00
21.3–39.5	0.64 (0.44, 0.94)	0.96 (0.64, 1.46)	—	0.84 (0.60, 1.17)	0.80 (0.48, 1.33)
39.6–2,721	0.93 (0.62, 1.40)	0.81 (0.55, 1.19)	—	0.96 (0.69, 1.34)	0.87 (0.53, 1.44)
Ln(MEHHP)	1.00 (0.84, 1.19)	0.95 (0.80, 1.13)	0.84	1.00 (0.86, 1.16)	1.04 (0.84, 1.30)
MECPP					
3.09–30.0	1.00	1.00	—	1.00	1.00
30.1–52.1	0.74 (0.51, 1.09)	0.67 (0.44, 1.02)	—	0.73 (0.52, 1.02)	0.85 (0.51, 1.42)
2.2–1,950	0.91 (0.61, 1.37)	0.60 (0.40, 0.90)	—	0.80 (0.57, 1.13)	0.93 (0.56, 1.53)
Ln(MECPP)	0.94 (0.77, 1.14)	0.85 (0.71, 1.02)	0.98	0.87 (0.74, 1.02)	0.93 (0.73, 1.19)

Note: LIBCSP women without breast cancer were age-matched to women diagnosed with breast cancer between 1 August 1996 and 31 July 1997. —, no information was collected at that particular examination point; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; MBzP, monobenzyl phthalate; MCNP, monocarboxy-isononyl phthalate; MCOP, monocarboxyoctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*N*-butyl phthalate; MWP, molecular-weight phthalate; OR, unconditional logistic regression odds ratio.

[a]Tertiles (μg/g creatinine) based on distributions among women without breast cancer.

[b]Adjusted for age (continuous), age at menarche (continuous), education (< high school/high school graduate, college, and postcollege), menopausal status (pre- vs. postmenopausal), hormone replacement therapy use (never vs. ever), body mass index (< 25.0, 25.0–29.9, and ≥ 30.0 kg/m²), and oral contraceptive use (never vs. ever), as appropriate.

[c]$P_{Interaction}$ derived from continuous BMI by continuous phthalate metabolite concentration interactions in the logistic regression models.

[d]MCOP and MCNP were measured in 320 women with BC and 205 women without BC only.

[e]Low MWP: Creatinine-corrected molar sum of MEP, MnBP, and MiBP (expressed as MEP, molecular weight 194).

[f]High MWP: Creatinine-corrected molar sum of MBzP, MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

[g]ΣDEHP: Creatinine-corrected molar sum of DEHP metabolites: MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

Table 3. (*Continued.*)

Analyte[a]	Body mass index (BMI) [OR (95% CI)][b]			ER status [OR (95% CI)][b]	
	<25.0 kg/m^2 (n = 306 BC vs. no BC = 293)	≥25.0 kg/m^2 (n = 376 BC vs. no BC = 265)	$P_{Interaction}$[c]	ER + (n = 354 BC vs. no BC = 558)	ER − (n = 109 BC vs. no BC = 558)
Low MWP[e]					
24.5–141	1.00	1.00	—	1.00	1.00
141–335	0.82 (0.55, 1.22)	0.61 (0.41, 0.91)	—	0.68 (0.49, 0.96)	0.55 (0.33, 0.94)
337–34,163	1.05 (0.71, 1.56)	0.71 (0.48, 1.05)	—	0.79 (0.57, 1.10)	0.82 (0.51, 1.33)
Ln(Low MWP)	0.98 (0.85, 1.12)	0.88 (0.76, 1.01)	0.30	0.90 (0.79, 1.01)	0.94 (0.78, 1.13)
High MWP[f]					
7.36–81.2	1.00	1.00	—	1.00	1.00
82.0–139	0.66 (0.45, 0.96)	0.96 (0.64, 1.45)	—	0.82 (0.58, 1.14)	1.00 (0.61, 1.65)
140–6,320	0.86 (0.58, 1.29)	0.79 (0.53, 1.17)	—	0.92 (0.66, 1.28)	0.81 (0.48, 1.36)
Ln(High MWP)	0.94 (0.77, 1.15)	0.92 (0.76, 1.11)	0.91	0.94 (0.79, 1.11)	0.96 (0.74, 1.23)
ΣDEHP[g]					
5.45–63.0	1.00	1.00		1.00	1.00
63.3–116	0.88 (0.60, 1.28)	0.85 (0.56, 1.28)		0.91 (0.65, 1.27)	0.95 (0.58, 1.57)
117–6,265	0.89 (0.59, 1.34)	0.74 (0.50, 1.10)		0.92 (0.66, 1.30)	0.83 (0.50, 1.39)
Ln(ΣDEHP)	0.96 (0.80, 1.17)	0.89 (0.74, 1.07)	0.93	0.93 (0.79, 1.09)	0.98 (0.77, 1.24)

In the subsample of women in this study, 65.4% were postmenopausal at diagnosis, 93.1% self-identified as white, and participants ranged in age from 22–96 y at diagnosis or selection. The mean age at diagnosis among women with BC was 59.1 y (SD = 12.8). There were small differences in the distribution of characteristics among the women with available values of urinary concentrations of phthalate metabolites and the full LIBCSP sample. Compared to the full sample of women without BC, lower proportions of women without BC included in this ancillary study were aged ≥65 y (25.3% vs. 28.3%) and were postmenopausal at diagnosis (62.8% vs. 66.3%). Compared to the full sample of women with BC, higher proportions of women with BC included in this ancillary study had nodal involvement (78.0% vs. 74.5%) and were diagnosed with ER + BC (76.1% vs. 73.3%); ER status was missing for 32% of women with BC. Approximately 82% of the women with BC included in this ancillary study provided urine samples prior to chemotherapy treatment.

Concentrations of most phthalate metabolites were similar, except for MEP for which the median concentrations were 10- to 100-fold higher relative to the other metabolites (Table S1). Because MCOP and MCNP were only analyzed in the second batch, data for these metabolites were missing for more than half of participants. The concentrations and concentration patterns we observed in our study are also similar to those reported among adult women for four phthalate metabolites (MEP, MnBP, MBzP, MEHP) available in the 1999–2000 National Health and Nutrition Examination Survey (Table S1) (CDC 2001).

Among the women without BC, we observed high correlations between MEHP and other DEHP metabolites, specifically MEHHP (r_P = 0.90), MEOHP (r_P = 0.86), and MECPP (r_P = 0.65), and also between MCNP and MCPP (r_P = 0.58) (all $p < 0.05$) (Table S3). Creatinine-corrected metabolite concentrations were weakly correlated with continuous covariates; at diagnosis, BMI (kg/m^2) was positively correlated with MEOHP (r_P = 0.09) and MECPP (r_P = 0.10) (both $p < 0.05$). Continuous creatinine-corrected concentrations of MCPP were inversely correlated with age at menarche ($r_P = -0.10$; $p < 0.05$). Quintiles of several metabolites were statistically significantly associated with categorized age at reference (MCPP and MEHP), BMI (MEOHP and MEHHP), education (MiBP), income (MiBP and MEHP), menopausal status (MCPP, MCNP, and MECPP), and hormone replacement therapy use (MEP) (all chi-squared $p < 0.05$) (Table S4). In analyses in which we examined the receipt of chemotherapy treatment prior to urine sample collection, we found that chemotherapy was associated with lower concentrations of MEP and higher levels of MBZP and MEHHP (Table S5). Given these findings, all multivariable Cox regression models were adjusted for receipt of chemotherapy treatment prior to sample collection. Last, in analyses in which we examined phthalate metabolite concentrations in association with disease and treatment characteristics, we found that MCOP, MEHP, MEOHP, MEHHP, and MECPP concentrations differed by stage (*in situ* vs. invasive), and MBzP, MEOHP, and MEHHP concentrations differed by receipt of chemotherapy treatment, based on statistically significant mean differences derived from generalized linear models regressing each of the ln-transformed creatinine-corrected phthalate metabolite concentrations on age and the covariate (Table S6). Phthalate metabolite concentrations did not differ by tumor size, nodal involvement, ER status, and radiation and hormone therapies.

Case–Control Analyses

The case–control results examining associations between urinary phthalate metabolite concentrations and BC are presented in Table 2. Compared to the lowest quintiles, the highest quintiles of all phthalate metabolites were not associated with increased odds of BC; the fully adjusted ORs in the highest quintiles were all close to or below one. The largest inverse associations were for MCPP, MBzP, MCNP, and MCOP for which the highest quintiles were associated with ORs of BC of 0.71 (95% CI: 0.49, 1.01), 0.72 (95% CI: 0.50, 1.03), 0.72 (95% CI: 0.40, 1.03), and 0.73 (95% CI: 0.71, 1.30), respectively, relative to the lowest quintiles. Continuous ln-transformed concentrations of MCPP were inversely associated with BC (OR = 0.85; 95% CI: 0.72, 1.00).

The case–control results examining effect modification by BMI and associations with BC subtype are presented in Table 3. Overall, there was little evidence of effect modification by BMI or heterogeneity by ER status.

Follow-up Analyses

Among the 710 women with BC, we identified 271 deaths, including 20 deaths among women with *in situ* disease, at the end of follow-up (median duration = 17.6 y; max = 18.4 y). Of the 271 deaths, 98 were related to BC, including three BC-related deaths among women with *in situ* disease. Cause of death was missing for eight women. The follow-up results examining associations between urinary phthalate metabolite concentrations and all-cause and BC-specific survival following BC are presented in

Table 4. Associations between urinary phthalate metabolite concentrations (μg/g creatinine) and mortality in the Long Island Breast Cancer Study Project (LIBCSP) women diagnosed with breast cancer in 1996–1997 and followed for 18 + y ($n = 710$).

	All-cause mortality [HR (95% CI)][a]				Breast cancer–specific mortality [HR (95% CI)][b]			
Analyte[d]	Deaths	Censored	Age adjusted	Multivariable adjusted[c]	Deaths	Censored	Age adjusted	Multivariable adjusted[c]
MEP								
Quintile 1	66	108	1.00	1.00	28	146	1.00	1.00
Quintile 2	57	86	0.98 (0.69, 1.40)	1.00 (0.69, 1.45)	16	126	0.70 (0.38, 1.29)	0.91 (0.48, 1.73)
Quintile 3	58	62	1.28 (0.90, 1.83)	1.37 (0.95, 1.98)	24	93	1.31 (0.76, 2.26)	1.52 (0.84, 2.73)
Quintile 4	40	92	0.83 (0.56, 1.23)	0.84 (0.56, 1.27)	14	116	0.65 (0.34, 1.23)	0.78 (0.40, 1.52)
Quintile 5	50	91	0.88 (0.61, 1.27)	0.91 (0.62, 1.34)	16	123	0.69 (0.37, 1.27)	0.81 (0.42, 1.56)
Ln(MEP)	—	—	0.98 (0.90, 1.08)	1.00 (0.91, 1.09)	—	—	0.93 (0.80, 1.08)	0.97 (0.83, 1.13)
MnBP								
Quintile 1	67	103	1.00	1.00	28	141	1.00	1.00
Quintile 2	47	78	0.85 (0.59, 1.24)	0.92 (0.63, 1.35)	25	98	1.22 (0.71, 2.10)	1.36 (0.77, 2.39)
Quintile 3	64	91	0.89 (0.63, 1.25)	0.94 (0.65, 1.34)	19	135	0.72 (0.40, 1.29)	0.77 (0.42, 1.43)
Quintile 4	45	72	0.80 (0.55, 1.16)	0.83 (0.55, 1.24)	10	105	0.50 (0.24, 1.03)	0.53 (0.24, 1.14)
Quintile 5	48	95	0.81 (0.56, 1.18)	0.85 (0.57, 1.24)	16	125	0.66 (0.36, 1.22)	0.69 (0.36, 1.32)
Ln(MnBP)	—	—	0.96 (0.83, 1.11)	0.99 (0.85, 1.15)	—	—	0.80 (0.63, 1.01)	0.83 (0.65, 1.07)
MiBP								
Quintile 1	68	105	1.00	1.00	29	142	1.00	1.00
Quintile 2	52	88	0.91 (0.64, 1.31)	0.90 (0.62, 1.31)	16	123	0.67 (0.36, 1.22)	0.66 (0.35, 1.25)
Quintile 3	62	78	1.32 (0.93, 1.86)	1.30 (0.90, 1.87)	22	116	0.95 (0.55, 1.66)	0.93 (0.52, 1.68)
Quintile 4	42	82	0.85 (0.58, 1.25)	0.84 (0.57, 1.25)	15	108	0.68 (0.37, 1.27)	0.66 (0.35, 1.26)
Quintile 5	47	86	0.91 (0.63, 1.32)	0.92 (0.63, 1.35)	16	115	0.69 (0.37, 1.27)	0.64 (0.34, 1.23)
Ln(MiBP)	—	—	0.97 (0.86, 1.09)	0.96 (0.85, 1.09)	—	—	0.91 (0.75, 1.11)	0.88 (0.71, 1.08)
MCPP								
Quintile 1	68	105	1.00	1.00	31	140	1.00	1.00
Quintile 2	49	83	0.77 (0.53, 1.12)	0.80 (0.55, 1.18)	16	116	0.64 (0.35, 1.17)	0.71 (0.38, 1.33)
Quintile 3	58	101	0.80 (0.56, 1.13)	0.82 (0.57, 1.18)	18	138	0.61 (0.34, 1.09)	0.62 (0.33, 1.17)
Quintile 4	42	75	0.80 (0.54, 1.17)	0.87 (0.59, 1.30)	16	101	0.72 (0.40, 1.32)	0.88 (0.48, 1.64)
Quintile 5	54	75	0.99 (0.69, 1.41)	0.98 (0.67, 1.43)	17	109	0.74 (0.41, 1.34)	0.75 (0.40, 1.40)
Ln(MCPP)	—	—	1.05 (0.88, 1.25)	1.04 (0.86, 1.25)	—	—	0.77 (0.57, 1.06)	0.82 (0.59, 1.14)
MBzP								
Quintile 1	66	117	1.00	1.00	27	155	1.00	1.00
Quintile 2	52	69	1.24 (0.86, 1.79)	1.20 (0.82, 1.75)	16	100	0.96 (0.52, 1.79)	0.91 (0.47, 1.74)
Quintile 3	63	96	1.24 (0.88, 1.75)	1.26 (0.88, 1.81)	25	134	1.13 (0.65, 1.94)	1.09 (0.61, 1.92)
Quintile 4	40	73	1.06 (0.71, 1.57)	1.00 (0.66, 1.51)	11	101	0.66 (0.33, 1.33)	0.54 (0.26, 1.14)
Quintile 5	50	84	1.13 (0.78, 1.63)	1.17 (0.80, 1.71)	19	114	0.99 (0.55, 1.79)	0.91 (0.49, 1.69)
Ln(MBzP)	—	—	1.03 (0.91, 1.17)	1.04 (0.91, 1.19)	—	—	0.97 (0.78, 1.19)	0.91 (0.72, 1.15)
MCOP[e]								
Quintile 1	31	47	1.00	1.00	17	60	1.00	1.00
Quintile 2	24	36	1.15 (0.68, 1.96)	1.21 (0.69, 2.13)	13	47	1.02 (0.50, 2.11)	1.15 (0.52, 2.52)
Quintile 3	26	34	1.15 (0.68, 1.94)	1.02 (0.59, 1.78)	9	48	0.72 (0.32, 1.62)	0.64 (0.27, 1.55)
Quintile 4	28	28	1.05 (0.62, 1.76)	1.07 (0.61, 1.86)	9	47	0.71 (0.32, 1.60)	0.72 (0.29, 1.77)
Quintile 5	27	39	0.96 (0.57, 1.61)	0.99 (0.58, 1.70)	8	58	0.51 (0.22, 1.18)	0.55 (0.23, 1.35)
Ln(MCOP)	—	—	0.98 (0.83, 1.16)	1.00 (0.84, 1.20)	—	—	0.75 (0.56, 0.99)	0.77 (0.56, 1.05)
MCNP[e]								
Quintile 1	30	43	1.00	1.00	18	55	1.00	1.00
Quintile 2	17	22	1.20 (0.66, 2.18)	1.40 (0.76, 2.59)	6	33	0.65 (0.26, 1.64)	0.82 (0.31, 2.14)
Quintile 3	21	43	0.83 (0.47, 1.44)	0.93 (0.52, 1.67)	6	58	0.35 (0.14, 0.89)	0.45 (0.17, 1.17)
Quintile 4	44	42	1.36 (0.85, 2.16)	1.44 (0.87, 2.39)	20	64	0.99 (0.52, 1.87)	1.11 (0.55, 2.27)
Quintile 5	24	34	1.13 (0.66, 1.94)	1.29 (0.73, 2.27)	6	50	0.41 (0.16, 1.03)	0.52 (0.20, 1.37)
Ln(MCNP)	—	—	1.03 (0.85, 1.24)	1.06 (0.87, 1.30)	—	—	0.78 (0.56, 1.08)	0.87 (0.62, 1.22)
MEHP								
Quintile 1	81	84	1.00	1.00	35	129	1.00	1.00
Quintile 2	55	83	0.74 (0.52, 1.04)	0.73 (0.51, 1.04)	16	120	0.51 (0.28, 0.92)	0.51 (0.27, 0.96)
Quintile 3	45	92	0.69 (0.48, 1.00)	0.73 (0.50, 1.07)	17	118	0.55 (0.31, 0.99)	0.65 (0.35, 1.18)

Note: LIBCSP participants diagnosed with breast cancer between 1 August 1996 and 31 July 1997 followed-up for vital status through December 31, 2014. Women alive at the end of follow-up were censored at the end of follow-up. For breast cancer–specific mortality, non–breast cancer deaths were censored at the time of death. —, no information was collected at that particular examination point; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; HR, hazard ratio; MBzP, monobenzyl phthalate; MCNP, monocarboxy-isononyl phthalate; MCOP, monocarboxyoctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*N*-butyl phthalate; MWP, molecular-weight phthalate.

[a]Age-adjusted models based on 271 deaths and 439 censored observations, and multivariable-adjusted models based on 255 deaths and 416 censored observations due to missing covariate data.

[b]Age-adjusted models based on 98 deaths and 604 censored observations, and multivariable-adjusted models based on 90 deaths and 575 censored observations due to missing covariate data.

[c]Adjusted for age (continuous), education ($<$ high school/high school graduate, college, and postcollege), menopausal status (pre- vs. postmenopausal), hormone replacement therapy use (never vs. ever), body mass index (<25.0, 25.0–29.9, and $\geq 30.0\,\mathrm{kg/m^2}$), oral contraceptive use (never vs. ever), and receipt of hemotherapy treatment prior to urine sample collection (yes vs. no).

[d]Quintiles (μg/g creatinine) based on distributions among women without breast cancer.

[e]MCOP and MCNP were measured in 320 women with BC only.

[f]Low MWP: Creatinine-corrected molar sum of MEP, MnBP, and MiBP (expressed as MEP, molecular weight 194).

[g]High MWP: Creatinine-corrected molar sum of MBzP, MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

[h]ΣDEHP: Creatinine-corrected molar sum of DEHP metabolites: MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

Table 4. (*Continued.*)

Analyte[d]	All-cause mortality [HR (95% CI)][a]				Breast cancer–specific mortality [HR (95% CI)][b]			
	Deaths	Censored	Age adjusted	Multivariable adjusted[c]	Deaths	Censored	Age adjusted	Multivariable adjusted[c]
Quintile 4	41	105	0.62 (0.43, 0.91)	0.68 (0.46, 1.00)	15	131	0.44 (0.24, 0.82)	0.47 (0.25, 0.89)
Quintile 5	49	75	0.89 (0.62, 1.27)	0.87 (0.60, 1.27)	15	106	0.57 (0.31, 1.04)	0.54 (0.28, 1.04)
Ln(MEHP)	—	—	0.95 (0.84, 1.07)	0.95 (0.84, 1.08)	—	—	0.80 (0.66, 0.98)	0.79 (0.64, 0.98)
MEOHP								
Quintile 1	52	92	1.00	1.00	21	122	1.00	1.00
Quintile 2	54	104	0.82 (0.56, 1.20)	0.77 (0.52, 1.15)	22	134	0.92 (0.51, 1.67)	0.78 (0.41, 1.49)
Quintile 3	56	67	1.18 (0.81, 1.72)	1.12 (0.75, 1.66)	16	106	0.89 (0.47, 1.71)	0.82 (0.41, 1.62)
Quintile 4	58	91	1.03 (0.71, 1.49)	1.01 (0.69, 1.50)	22	126	1.02 (0.56, 1.85)	0.94 (0.50, 1.77)
Quintile 5	51	85	1.04 (0.71, 1.53)	0.96 (0.63, 1.44)	17	116	0.87 (0.46, 1.66)	0.70 (0.35, 1.40)
Ln(MEOHP)	—	—	1.04 (0.91, 1.19)	1.03 (0.89, 1.19)	—	—	0.97 (0.78, 1.21)	0.92 (0.72, 1.16)
MEHHP								
Quintile 1	55	92	1.00	1.00	22	124	1.00	1.00
Quintile 2	44	103	0.69 (0.47, 1.03)	0.72 (0.48, 1.09)	15	131	0.64 (0.33, 1.23)	0.71 (0.35, 1.44)
Quintile 3	65	69	1.32 (0.92, 1.88)	1.32 (0.91, 1.92)	26	106	1.36 (0.77, 2.39)	1.51 (0.82, 2.76)
Quintile 4	52	88	0.99 (0.68, 1.44)	1.02 (0.69, 1.52)	18	121	0.86 (0.46, 1.59)	0.90 (0.46, 1.77)
Quintile 5	55	87	1.11 (0.76, 1.61)	1.06 (0.71, 1.58)	17	122	0.82 (0.44, 1.54)	0.77 (0.39, 1.55)
Ln(MEHHP)	—	—	1.07 (0.94, 1.22)	1.05 (0.91, 1.21)	—	—	0.97 (0.79, 1.21)	0.93 (0.74, 1.17)
MECPP								
Quintile 1	56	96	1.00	1.00	27	125	1.00	1.00
Quintile 2	63	110	0.83 (0.58, 1.19)	0.82 (0.56, 1.20)	21	150	0.66 (0.37, 1.16)	0.72 (0.39, 1.32)
Quintile 3	37	75	0.82 (0.54, 1.25)	0.83 (0.53, 1.28)	12	99	0.60 (0.30, 1.18)	0.61 (0.30, 1.27)
Quintile 4	61	78	1.12 (0.78, 1.62)	1.12 (0.76, 1.64)	22	114	0.94 (0.54, 1.66)	1.00 (0.55, 1.83)
Quintile 5	54	80	1.02 (0.70, 1.49)	1.00 (0.67, 1.49)	16	116	0.68 (0.37, 1.26)	0.62 (0.31, 1.22)
Ln(MECPP)	—	—	1.06 (0.92, 1.22)	1.05 (0.90, 1.23)	—	—	0.93 (0.73, 1.18)	0.90 (0.70, 1.16)
Low MWP[f]								
Quintile 1	62	101	1.00	1.00	20	143	1.00	1.00
Quintile 2	66	108	0.99 (0.70, 1.40)	1.04 (0.72, 1.49)	24	149	1.10 (0.61, 1.99)	1.28 (0.67, 2.43)
Quintile 3	53	50	1.61 (1.11, 2.32)	1.78 (1.21, 2.62)	25	76	2.23 (1.24, 4.01)	2.71 (1.44, 5.09)
Quintile 4	38	88	0.87 (0.58, 1.31)	0.90 (0.59, 1.38)	12	111	0.75 (0.37, 1.54)	0.92 (0.44, 1.93)
Quintile 5	52	92	0.95 (0.65, 1.37)	0.99 (0.68, 1.45)	17	125	0.94 (0.49, 1.80)	1.11 (0.56, 2.20)
Ln(Low MWP)	—	—	0.99 (0.89, 1.10)	1.00 (0.90, 1.11)	—	—	0.92 (0.77, 1.10)	0.96 (0.80, 1.16)
High MWP[g]								
Quintile 1	58	94	1.00	1.00	24	127	1.00	1.00
Quintile 2	57	104	0.90 (0.62, 1.30)	0.94 (0.64, 1.37)	21	138	0.81 (0.45, 1.46)	0.83 (0.45, 1.56)
Quintile 3	50	68	1.14 (0.78, 1.66)	1.11 (0.75, 1.65)	19	98	1.04 (0.57, 1.89)	1.07 (0.57, 2.02)
Quintile 4	46	87	0.87 (0.59, 1.27)	0.92 (0.61, 1.37)	14	117	0.66 (0.34, 1.28)	0.71 (0.36, 1.43)
Quintile 5	60	86	1.19 (0.83, 1.70)	1.12 (0.76, 1.66)	20	124	0.90 (0.50, 1.62)	0.73 (0.36, 1.43)
Ln(High MWP)	—	—	1.06 (0.91, 1.22)	1.05 (0.90, 1.23)	—	—	0.93 (0.73, 1.18)	0.87 (0.67, 1.13)
ΣDEHP[h]								
Quintile 1	56	89	1.00	1.00	23	121	1.00	1.00
Quintile 2	55	113	0.68 (0.47, 0.98)	0.70 (0.47, 1.03)	21	145	0.74 (0.41, 1.34)	0.86 (0.45, 1.63)
Quintile 3	45	70	0.96 (0.65, 1.43)	0.94 (0.63, 1.42)	14	100	0.77 (0.40, 1.50)	0.80 (0.39, 1.65)
Quintile 4	62	84	1.04 (0.73, 1.50)	1.11 (0.76, 1.62)	22	122	0.97 (0.54, 1.74)	1.14 (0.60, 2.15)
Quintile 5	53	83	0.94 (0.65, 1.38)	0.89 (0.60, 1.34)	18	116	0.84 (0.45, 1.55)	0.77 (0.39, 1.52)
Ln(ΣDEHP)	—	—	1.06 (0.92, 1.22)	1.05 (0.90, 1.22)	—	—	0.94 (0.74, 1.19)	0.90 (0.70, 1.16)

Table 4. Compared to the lowest quintiles, the highest quintiles of all phthalate metabolites were not associated with increased risk of mortality following BC; all HRs in the highest quintiles were close to or below one. The largest inverse associations were for MEHP and MCOP for which the highest quintiles were associated with HRs of BC-specific mortality of 0.54 (95% CI: 0.28, 1.04) and 0.55 (95% CI: 0.23, 1.35), respectively, relative to the lowest quintiles. However, the estimate for MCOP was imprecise due to the availability of data for this metabolite for 320 women with BC. Continuous ln-transformed concentrations of MEHP and MCOP were also inversely associated with BC-specific mortality ($HR_{Ln(MEHP)} = 0.79$, 95% CI: 0.64, 0.98; and $HR_{Ln(MCOP)} = 0.77$, 95% CI: 0.56, 1.05). The associations between MEHP and MCOP were stronger when we considered mortality within 5 y of BC diagnosis (Table 5); continuous ln-transformed MEPH and MCOP were associated with HRs of BC-specific mortality of 0.75 (95% CI: 0.56, 100) and 0.54 (95% CI: 0.33, 0.89), though estimates were imprecise. At 5 y postdiagnosis, the highest tertile of MiBP was also associated with a HR of BC-specific mortality of 0.48 (95% CI: 0.22, 1.03); continuous ln-transformed MiBP concentrations were associated with a HR of BC-specific mortality of 0.75 (95% CI: 0.56, 0.99).

The follow-up results examining effect modification by BMI and ER status are presented in Table 6. There was little evidence of effect modification by ER status; however, ER status and cause of death were only available for 476 (67%) of the 710 women with BC. We observed effect modification by BMI for MEOHP ($P_{Interaction} = 0.04$), MEHHP ($P_{Interaction} = 0.04$), MECPP ($P_{Interaction} = 0.01$), the sum of the HMWPs ($P_{Interaction} = 0.01$), and the sum of DEPH metabolites ($P_{Interaction} = 0.02$). Associations were positive among women with BMI $<25\,kg/m^2$ and inverse among women with BMI $\geq 25.0\,kg/m^2$.

Discussion

In this study of predominantly white women, urinary concentrations of phthalate metabolites were not associated with increased odds of BC. In our study, the highest quintiles of MCPP, MBzP, and MCOP were associated with ORs of BC ranging from 0.71 to 0.73, compared to the lowest quintiles. The continuous concentrations of MCPP were associated with ORs of BC of 0.85 for a one-unit increase in ln-transformed MCPP concentrations. In the case–control analyses, we observed little evidence of

Table 5. Associations between urinary phthalate metabolite concentrations (μg/g creatinine) and 5-y mortality in the Long Island Breast Cancer Study Project (LIBCSP) women diagnosed with breast cancer in 1996–1997 ($n = 710$).

	All-cause mortality[a]			Breast cancer–specific mortality[b]		
Analyte[c]	Deaths	Censored	HR (95% CI)[d]	Deaths	Censored	HR (95% CI)[d]
MEP						
Tertile 1	31	243	1.00	22	251	1.00
Tertile 2	27	184	1.16 (0.67, 2.01)	20	186	1.42 (0.75, 2.69)
Tertile 3	17	208	0.78 (0.69, 1.43)	9	214	0.60 (0.27, 1.32)
Ln(MEP)	—	—	1.01 (0.85, 1.21)	—	—	0.91 (0.73, 1.14)
MnBP						
Tertile 1	31	222	1.00	23	228	1.00
Tertile 2	24	205	0.69 (0.39, 1.22)	17	208	0.76 (0.40, 1.47)
Tertile 3	20	208	0.75 (0.42, 1.35)	11	215	0.53 (0.25, 1.13)
Ln(MnBP)	—	—	0.94 (0.70, 1.24)	—	—	0.82 (0.58, 1.15)
MiBP						
Tertile 1	32	239	1.00	25	243	1.00
Tertile 2	25	204	0.98 (0.57, 1.70)	15	211	0.78 (0.41, 1.51)
Tertile 3	18	192	0.64 (0.34, 1.18)	11	197	0.48 (0.22, 1.03)
Ln(MiBP)	—	—	0.85 (0.67, 1.08)	—	—	0.75 (0.56, 0.99)
MCPP						
Tertile 1	30	213	1.00	21	220	1.00
Tertile 2	22	248	0.72 (0.40, 1.28)	14	253	0.70 (0.35, 1.40)
Tertile 3	23	174	0.97 (0.54, 1.72)	16	178	0.92 (0.46, 1.82)
Ln(MCPP)	—	—	0.96 (0.66, 1.39)	—	—	0.92 (0.59, 1.43)
MBzP						
Tertile 1	21	248	1.00	15	249	1.00
Tertile 2	33	206	1.90 (1.06, 3.43)	25	213	1.78 (0.91, 3.47)
Tertile 3	21	181	1.45 (0.76, 2.75)	11	189	0.88 (0.39, 1.99)
Ln(MBzP)	—	—	1.04 (0.80, 1.36)	—	—	0.88 (0.64, 1.22)
MCOP[e]						
Tertile 1	17	104	1.00	15	105	1.00
Tertile 2	21	82	1.31 (0.65, 2.62)	14	86	0.99 (0.45, 2.17)
Tertile 3	<5	92	Not determined	<5	94	Not determined
Ln(MCOP)	—	—	0.59 (0.40, 0.89)	—	—	0.54 (0.33, 0.89)
MCNP[e]						
Tertile 1	16	81	1.00	12	85	1.00
Tertile 2	11	97	0.59 (0.27, 1.28)	6	101	0.45 (0.17, 1.21)
Tertile 3	15	100	0.80 (0.38, 1.69)	13	99	0.98 (0.43, 2.24)
Ln(MCNP)	—	—	0.78 (0.51, 1.19)	—	—	0.87 (0.55, 1.38)
MEHP						
Tertile 1	36	222	1.00	26	231	1.00
Tertile 2	18	205	0.69 (0.38, 1.25)	12	207	0.64 (0.32, 1.29)
Tertile 3	21	208	0.77 (0.44, 1.36)	13	213	0.57 (0.28, 1.16)
Ln(MEHP)	—	—	0.85 (0.67, 1.08)	—	—	0.75 (0.56, 1.00)
MEOHP						
Tertile 1	27	236	1.00	20	240	1.00
Tertile 2	24	189	1.28 (0.71, 2.32)	15	197	0.98 (0.48, 2.00)
Tertile 3	24	210	1.06 (0.59, 1.90)	16	214	0.95 (0.48, 1.88)
Ln(MEOHP)	—	—	0.89 (0.68, 1.18)	—	—	0.85 (0.61, 1.18)
MEHHP						
Tertile 1	26	235	1.00	19	240	1.00
Tertile 2	23	191	1.25 (0.68, 2.29)	16	196	1.08 (0.53, 2.19)
Tertile 3	26	209	1.23 (0.69, 2.20)	16	215	1.02 (0.51, 2.04)
Ln(MEHHP)	—	—	0.93 (0.71, 1.22)	—	—	0.88 (0.64, 1.21)
MECPP						
Tertile 1	24	245	1.00	20	247	1.00
Tertile 2	24	193	1.35 (0.74, 2.47)	12	203	0.78 (0.37, 1.66)

Note: LIBCSP participants diagnosed with breast cancer between 1 August 1996 and 31 July 1997 followed-up for vital status through December 31, 2014. Women alive at the end of follow-up were censored at the end of follow-up. For breast cancer–specific mortality, non–breast cancer deaths were censored at the time of death. —, no information was collected at that particular examination point; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; HR, hazard ratio; MBzP, monobenzyl phthalate; MCNP, monocarboxy-isononyl phthalate; MCOP, monocarboxyoctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*N*-butyl phthalate; MWP, molecular-weight phthalate.

[a]Multivariable-adjusted models based on 69 deaths and 602 censored observations due to missing covariate data.

[b]Multivariable-adjusted models based on 48 deaths and 617 censored observations due to missing covariate data.

[c]Tertiles (μg/g creatinine) based on distributions among women without breast cancer.

[d]Adjusted for age (continuous), education (< high school/high school graduate, college, and postcollege), menopausal status (pre- vs. postmenopausal), hormone replacement therapy use (never vs. ever), body mass index (< 25.0, 25.0–29.9, and $\geq 30.0\,kg/m^2$), oral contraceptive use (never vs. ever), and receipt of chemotherapy treatment prior to urine sample collection (yes vs. no).

[e]MCOP and MCNP were measured in 320 women with BC only.

[f]Low MWP: Creatinine-corrected molar sum of MEP, MnBP, and MiBP (expressed as MEP, molecular weight 194).

[g]High MWP: Creatinine-corrected molar sum of MBzP, MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

[h]ΣDEHP: Creatinine-corrected molar sum of DEHP metabolites: MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

Table 5. (*Continued.*)

Analyte[c]	All-cause mortality[a]			Breast cancer–specific mortality[b]		
	Deaths	Censored	HR (95% CI)[d]	Deaths	Censored	HR (95% CI)[d]
Tertile 3	27	197	1.38 (0.77, 2.47)	19	201	1.25 (0.65, 2.40)
Ln(MECPP)	—	—	0.92 (0.69, 1.24)	—	—	0.89 (0.62, 1.26)
Low MWP[f]						
Tertile 1	29	252	1.00	20	260	1.00
Tertile 2	29	168	1.57 (0.91, 2.73)	22	170	1.88 (0.99, 3.57)
Tertile 3	17	215	0.83 (0.45, 1.54)	9	221	0.64 (0.29, 1.42)
Ln(Low MWP)	—	—	0.99 (0.80, 1.22)	—	—	0.85 (0.65, 1.11)
High MWP[g]						
Tertile 1	27	236	1.00	21	239	1.00
Tertile 2	25	193	1.22 (0.69, 2.17)	17	200	0.99 (0.51, 1.92)
Tertile 3	23	206	0.89 (0.49, 1.62)	13	212	0.63 (0.31, 1.32)
Ln(High MWP)	—	—	0.90 (0.67, 1.23)	—	—	0.81 (0.56, 1.17)
ΣDEHP[h]						
Tertile 1	24	227	1.00	18	232	1.00
Tertile 2	26	212	1.26 (0.70, 2.29)	18	217	1.18 (0.59, 2.36)
Tertile 3	25	196	1.19 (0.66, 2.16)	15	202	1.03 (0.51, 2.09)
Ln(ΣDEHP)	—	—	0.90 (0.67, 1.21)	—	—	0.85 (0.60, 1.21)

effect measure modification ($p < 0.05$) by BMI or ER status. In the follow-up analyses, compared to the lowest quintiles, the highest quintiles of MEHP and MCOP were associated with HRs of BC-specific mortality of 0.54 and 0.55, respectively. Furthermore, we observed inverse associations between MEOHP and MEHHP, and MEHPP and the sum of HMWPs and the sum of DEHP phthalates and BC-specific mortality among women with BMI $\geq 25.0\,kg/m^2$, but not among women with BMI $<25.0\,kg/m^2$. To our knowledge, ours is the first study to examine urinary phthalate metabolite concentrations in relation to survival following BC.

Our results for MCPP and MBzP are in agreement with one previous case–control study by López-Carrillo and colleagues, which reported inverse associations between the highest (vs. lowest) tertiles of these phthalate metabolites and BC among 233 Mexican women with BC and 221 age-matched controls ($OR_{MCPP} = 0.44$, 95% CI: 0.24, 0.80; and $OR_{MBzP} = 0.46$, 95% CI = 0.27, 0.79) (López-Carrillo et al. 2010). López-Carrillo and colleagues also reported positive association between BC and the highest tertiles of MEP (OR = 2.20; 95% CI: 1.33, 3.63) and MECPP (OR = 1.68; 95% CI: 1.01, 2.78); however, in our larger study, we did not observe any increases in BC risk for either metabolite and observed an inverse association for MECPP. Also in contrast to our study are results from a more recent but small hospital-based case–control study of 170 Alaska-Native women (75 women with BC and 95 women without BC), which reported an increase in risk of developing BC for increasing MEHP concentrations (OR = 2.43; 95% CI: 1.12, 5.24) (Holmes et al. 2014). Reasons for these discrepancies are unclear but may be attributed to differences in study population racial/cultural compositions (i.e., Mexican, Alaska-Native, and postmenopausal white women), study design (i.e., use of first morning void versus untimed spot urine samples), or to noncausal explanations, including random error and bias due to uncontrolled confounding and other sources of error.

Phthalates and their metabolites are hypothesized to influence BC incidence and mortality due to their potential as endocrine disruptors—both as hormone agonists and antagonists (Brody and Rudel 2003). BBP, for example, shows weak estrogenic activity *in vitro* and also leads to demethylation of ERα promoter–associated CpG islands, resulting in increased ERα transcript expression (Kang and Lee 2005). Phthalate metabolites also bind to and activate the peroxisome proliferator–activated receptors (PPARs), nuclear transcription factors that play a key role in adipocyte differentiation, resulting in cell proliferation and in elevated oxidative stress (Hurst and Waxman 2003; Ito and Nakajima 2008). However, PPARs may also exert anti-inflammatory effects by inhibiting pro-inflammatory cytokines, adhesion molecules, and extracellular matrix proteins (Kostadinova et al. 2005). Despite the biological plausibility linking phthalates to potential increased risk of BC and mortality following BC, we did not observe increases in BC risk for any of the phthalate metabolites examined. On the contrary, we observed inverse associations between several phthalate metabolites and BC. PPAR-mediated inhibition of inflammation signaling, and thus inhibition of cancer development and progression, is one mechanism that may potentially explain the inverse associations (Kostadinova et al. 2005). Additionally, exposure to phthalates has been associated with reductions in serum testosterone in women (Meeker et al. 2009), including parent phthalates of metabolites for which we observed inverse associations (Borch et al. 2006; Lee and Koo 2007; Mylchreest et al. 2000). Our results of effect measure modification by BMI as a surrogate measure of adiposity, a source of hormones including estrogens and androgens (Pasquali 2006), further support an antiandrogenic pathway. Through this antiandrogenic pathway, exposure to phthalates could potentially inhibit BC progression; however, there is yet no clear understanding of the mechanism of androgen receptor signaling in BC (Garay and Park 2012).

Our study has several strengths, including the larger design and the use of biomarker assessment using biospecimens collected shortly after diagnosis among women with BC. However, several limitations should be noted. First, multiple measurements may be needed to adequately predict concentrations over a long time period because of the temporal variability in phthalate metabolite concentrations within individuals (Starling et al. 2015), though single measurements demonstrate fair within-person reproducibility for several phthalate biomarkers over several days and months (Dewalque et al. 2015; Frederiksen et al. 2013; Hauser et al. 2004; Hoppin et al. 2002) and years (Townsend et al. 2013), reflecting habitual use of personal care products and fairly consistent dietary patterns. Any exposure misclassification would likely bias results towards the null if it is nondifferential with respect to BC diagnosis/survival. However, results could be biased away from the null if BC disease, diagnosis, or treatment impact phthalate exposure or metabolite concentrations. The timing of the urine collection, which occurred on average 3 mo after diagnosis, may have

influenced the measured phthalate levels. For example, it is possible that after diagnosis, some women may have altered their behavior, including dietary intake. But given that the women with BC were diagnosed in the mid-1990s, before the onset of widespread public concern about phthalate exposure, it is highly unlikely that women specifically changed their behavior with the intention of altering their exposure to phthalates. However, it is possible that phthalate measures could have been influenced by chemotherapy or by other treatments or their side effects. In particular, symptoms related to BC or treatment could have influenced the dietary intake in general, thus altering exposure to phthalates. Second, because urinary phthalate metabolite concentrations reflect relatively short-term exposure to phthalates, which have short biological half-lives, metabolite concentrations

Table 6. Associations between urinary phthalate metabolite concentrations (μg/g creatinine) and breast cancer–specific mortality in the LIBCSP, stratified by body mass index (BMI) and estrogen receptor (ER) status.

	BMI ($n = 665$) [HR (95% CI)][b]			ER status ($n = 454$) [HR (95% CI)][d]		
Analyte[a]	$<25.0\,kg/m^2$ (n deaths = 30, n censored = 267)	$\geq 25.0\,kg/m^2$ (n deaths = 60, n censored = 308)	$P_{Interaction}$[c]	ER + (n deaths = 46, n censored = 300)	ER − (n deaths = 30, n censored = 78)	$P_{Interaction}$[c]
MEP						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	0.66 (0.26, 1.64)	1.40 (0.77, 2.55)	—	1.08 (0.55, 2.11)	1.51 (0.58, 3.97)	—
Tertile 3	0.72 (0.31, 1.67)	0.91 (0.47, 1.75)	—	0.75 (0.36, 1.59)	0.60 (0.23, 1.58)	—
Ln(MEP)	0.93 (0.71, 1.22)	0.98 (0.80, 1.21)	0.63	0.92 (0.72, 1.16)	0.94 (0.71, 1.25)	0.77
MnBP						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	0.54 (0.22, 1.34)	0.98 (0.55, 1.74)	—	0.57 (0.29, 1.15)	1.35 (0.56, 3.26)	—
Tertile 3	0.48 (0.20, 1.18)	0.58 (0.29, 1.16)	—	0.43 (0.21, 0.91)	0.85 (0.31, 2.32)	—
Ln(MnBP)	0.81 (0.53, 1.23)	0.87 (0.63, 1.19)	0.61	0.84 (0.59, 1.19)	0.99 (0.63, 1.57)	0.60
MiBP						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	0.99 (0.43, 2.29)	1.01 (0.55, 1.83)	—	0.99 (0.49, 2.00)	0.89 (0.38, 2.06)	—
Tertile 3	0.63 (0.24, 1.66)	0.75 (0.39, 1.43)	—	0.84 (0.41, 1.74)	0.56 (0.20, 1.59)	—
Ln(MiBP)	0.99 (0.69, 1.40)	0.86 (0.66, 1.11)	0.18	0.99 (0.75, 1.30)	0.92 (0.62, 1.37)	0.77
MCPP						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	0.89 (0.35, 2.26)	0.45 (0.25, 0.84)	—	0.46 (0.22, 0.95)	0.89 (0.34, 2.34)	—
Tertile 3	1.70 (0.72, 4.01)	0.48 (0.25, 0.94)	—	0.69 (0.34, 1.40)	0.88 (0.36, 2.19)	—
Ln(MCPP)	1.34 (0.79, 2.27)	0.62 (0.40, 0.95)	0.11	0.77 (0.48, 1.24)	0.96 (0.49, 1.87)	0.52
MBzP						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	0.84 (0.36, 2.12)	1.18 (0.65, 2.12)	—	1.22 (0.61, 2.46)	1.30 (0.53, 3.18)	—
Tertile 3	1.15 (0.49, 2.70)	0.73 (0.37, 1.47)	—	1.03 (0.49, 2.15)	0.62 (0.22, 1.77)	—
Ln(MBzP)	1.12 (0.79, 1.61)	0.82 (0.65, 1.12)	0.09	1.02 (0.74, 1.40)	0.88 (0.55, 1.42)	0.76
MEHP						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	1.06 (0.45, 2.53)	0.45 (0.23, 0.89)	—	0.84 (0.41, 1.71)	0.92 (0.34, 2.49)	—
Tertile 3	1.02 (0.41, 2.53)	0.57 (0.31, 1.04)	—	0.77 (0.38, 1.57)	0.90 (0.38, 2.11)	—
Ln(MEHP)	1.06 (0.75, 1.52)	0.68 (0.52, 0.89)	0.10	0.83 (0.62, 1.11)	0.89 (0.62, 1.28)	0.95
MEOHP						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	1.97 (0.85, 4.56)	1.10 (0.59, 2.04)	—	1.31 (0.66, 2.60)	1.62 (0.61, 4.34)	—
Tertile 3	1.23 (0.46, 3.32)	0.78 (0.42, 1.47)	—	0.64 (0.30, 1.37)	1.52 (0.61, 3.80)	—
Ln(MEOHP)	1.32 (0.91, 1.91)	0.76 (0.56, 1.04)	0.04	0.88 (0.64, 1.22)	1.01 (0.69, 1.47)	0.53
MEHHP						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	2.24 (0.96, 5.19)	0.91 (0.49, 1.71)	—	1.30 (0.64, 2.63)	1.46 (0.59, 3.62)	—
Tertile 3	1.24 (0.46, 3.36)	0.83 (0.45, 1.55)	—	0.83 (0.40, 1.75)	1.13 (0.45, 2.83)	—
Ln(MEHHP)	1.25 (0.87, 1.80)	0.82 (0.61, 1.09)	0.04	0.90 (0.66, 1.24)	1.02 (0.70, 1.47)	0.58
MECPP						
Tertile 1	1.00	1.00	—	1.00	1.00	—

Note: LIBCSP participants diagnosed with breast cancer between 1 August 1996 and 31 July 1997, followed-up for vital status through December 31, 2014. —, no information was collected at that particular examination point; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; HR, hazard ratio; MBzP, monobenzyl phthalate; MCNP, monocarboxy-isononyl phthalate; MCOP, monocarboxyoctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*N*-butyl phthalate; MWP, molecular-weight phthalate.

[a]Tertiles (μg/g creatinine) based on distributions among women without breast cancer.

[b]Adjusted for age (continuous), education (< high school/high school graduate, college, and postcollege), menopausal status (pre- vs. postmenopausal), hormone replacement therapy use (never vs. ever), oral contraceptive use (never vs. ever), and receipt of chemotherapy treatment prior to urine sample collection (yes vs. no).

[c]PInteraction derived from continuous BMI- and dichotomized ER by continuous phthalate metabolite concentration interactions in the Cox regression models.

[d]Adjusted for age (continuous), education (< high school/high school graduate, college, and postcollege), menopausal status (pre- vs. postmenopausal), hormone replacement therapy use (never vs. ever), body mass index (< 25.0, 25.0–29.9, and $\geq 30.0\,kg/m^2$), oral contraceptive use (never vs. ever), and receipt of chemotherapy treatment prior to urine sample collection (yes vs. no), as appropriate.

[e]Low MWP: Creatinine-corrected molar sum of MEP, MnBP, and MiBP (expressed as MEP, molecular weight 194).

[f]High MWP: Creatinine-corrected molar sum of MBzP, MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

[g]ΣDEHP: Creatinine-corrected molar sum of DEHP metabolites: MEHP, MEOHP, MEHHP, MECPP (expressed as MEHP, molecular weight 278).

Table 6. (*Continued.*)

Analyte[a]	BMI ($n=665$) [HR (95% CI)][b]			ER status ($n=454$) [HR (95% CI)][d]		
	$<25.0\,kg/m^2$ (n deaths = 30, n censored = 267)	$\geq 25.0\,kg/m^2$ (n deaths = 60, n censored = 308)	$P_{Interaction}$[c]	ER + (n deaths = 46, n censored = 300)	ER − (n deaths = 30, n censored = 78)	$P_{Interaction}$[c]
Tertile 2	1.35 (0.53, 3.44)	0.53 (0.27, 1.04)	—	0.85 (0.41, 1.75)	0.45 (0.15, 1.33)	—
Tertile 3	2.39 (1.01, 5.67)	0.69 (0.39, 1.25)	—	0.93 (0.46, 1.86)	1.29 (0.56, 2.95)	—
Ln(MECPP)	1.40 (0.96, 2.06)	0.71 (0.51, 0.99)	0.01	0.85 (0.59, 1.22)	1.06 (0.71, 1.60)	0.40
Low MWP[e]						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	1.17 (0.49, 2.81)	2.12 (1.16, 3.89)	—	1.79 (0.91, 3.52)	1.74 (0.66, 4.63)	—
Tertile 3	0.83 (0.35, 1.98)	1.06 (0.54, 2.07)	—	0.93 (0.43, 2.01)	0.81 (0.32, 2.09)	—
Ln(Low MWP)	0.94 (0.69, 1.29)	0.97 (0.76, 1.23)	0.55	0.93 (0.70, 1.22)	0.94 (0.68, 1.30)	0.87
High MWP[f]						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	2.33 (1.01, 5.35)	0.76 (0.42, 1.38)	—	1.05 (0.53, 2.11)	1.04 (0.43, 2.49)	—
Tertile 3	1.27 (0.47, 3.44)	0.53 (0.28, 1.01)	—	0.77 (0.37, 1.61)	0.76 (0.30, 1.94)	—
Ln(High MWP)	1.34 (0.90, 2.00)	0.70 (0.49, 0.98)	0.01	0.86 (0.60, 1.23)	1.02 (0.66, 1.56)	0.50
ΣDEHP[g]						
Tertile 1	1.00	1.00	—	1.00	1.00	—
Tertile 2	2.21 (0.95, 5.15)	1.00 (0.55, 1.83)	—	1.25 (0.63, 2.49)	1.17 (0.47, 2.91)	—
Tertile 3	1.43 (0.52, 3.94)	0.70 (0.37, 1.34)	—	0.76 (0.36, 1.63)	1.15 (0.45, 2.93)	—
Ln(ΣDEHP)	1.34 (0.91, 1.96)	0.73 (0.53, 1.02)	0.02	0.87 (0.61, 1.24)	1.02 (0.68, 1.51)	0.53

may not relate to the etiologically relevant time period for the initiation of BC; the latent period for BC may be several decades (Terry et al. 2002). However, because of their potential as endocrine disruptors, phthalates may promote BC cell proliferation, migration, and invasion (Hsieh et al. 2012). Thus, assessment of phthalate exposure at the time of BC diagnosis may still be relevant to BC progression and survival. Third, in this study, we included a subsample of the population-based LIBCSP sample. Although we observed small differences between the women included in this study and the full LIBCSP sample and we adjusted our models for menopausal status for which we observed the largest difference between women without BC who were included in the present ancillary study and the full LIBCSP sample, there is a potential for selection bias. Fourth, there may be misclassification of BC-specific deaths. Fifth, although we were interested in examining associations between phthalate metabolites and BC mortality stratified by BC subtype, ER status was missing for 228 of the 710 women with BC included in this study, limiting our power to detect differences by ER status. Last, we cannot fully rule out residual and unmeasured confounding as a source of bias in this observational study. However, we examined a comprehensive list of covariates as potential confounders.

Conclusion

Our results overall do not support a hypothesized positive link between exposure to phthalates and breast carcinogenesis and progression. However, consistent with laboratory evidence and thus biologically plausible, we observed inverse associations between urinary concentrations of several phthalate metabolites and BC and subsequent BC-specific mortality among a sample of predominantly white women. Even so, these results should be interpreted with caution given that biospecimen collection among women with BC occurred after their diagnosis, which may be of concern particularly for our case–control findings.

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