

Research article

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# Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Cohort

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## Abstract

**Background:** Multidisciplinary attempts to understand the etiology of breast cancer are expanding to increasingly include new potential markers of disease risk. Those efforts may have maximal scientific and practical influence if new findings are placed in context of the well-understood lifestyle and reproductive risk factors or existing risk prediction models for breast cancer. We therefore evaluated known risk factors for breast cancer in a cancer screening trial that does not have breast cancer as a study endpoint but is large enough to provide numerous analytic opportunities for breast cancer.

**Methods:** We evaluated risk factors for breast cancer (N = 2085) among 70,575 women who were randomized in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Using Poisson regression, we calculated adjusted relative risks [RRs, with 95% confidence intervals (CIs)] for lifestyle and reproductive factors during an average of 5 years of follow-up from date of randomization.

**Results:** As expected, increasing age, nulliparity, positive family history of breast cancer, and use of menopausal hormone therapy were positively associated with breast cancer. Later age at

menarche (16 years or older vs. < 12: RR = 0.81, 95% CI, 0.65–1.02) or menopause (55 years or older vs. < 45: RR = 1.29, 95% CI, 1.03–1.62) were less strongly associated with breast cancer than was expected. There were weak positive associations between taller height and heavier weight, and only severe obesity [body mass index (BMI; kg/m<sup>2</sup>) 35 or more vs. 18.5–24.9: RR = 1.21, 95% CI, 1.02–1.43] was statistically significantly associated with breast cancer.

**Conclusion:** The ongoing PLCO trial offers continued opportunities for new breast cancer investigations, but these analyses suggest that the associations between breast cancer and age at menarche, age at menopause, and obesity might be changing as the underlying demographics of these factors change.

**Clinical Trials Registration:** <http://www.clinicaltrials.gov>, NCT00002540.

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## Background

Environment, genes, and lifestyle work together to increase or decrease the probability of developing female breast cancer [1]. Events early and late in life consistently influence breast cancer risk [2], but it remains difficult to explain why some women develop breast cancer and others do not [3]. This complicates prevention, yet some groups consistently have notably higher risks than other groups: women whose relatives have breast cancer [4], who first give birth later in life [5], who use exogenous hormones for extended durations [6], and who are overweight or obese after menopause [7].

Most of these conclusions were drawn from individual studies conducted in the 1970s through the late 1990s, or collaborative efforts to quantify risk across many studies [8-10]. Whereas many early studies were exploratory (because risk factor associations were less clear) contemporary studies can have additional or alternative aims, such as searching for molecular markers, evaluating risk among younger women or under-studied racial/ethnic groups, or testing new and refined risk prediction models. Expanding the breast cancer literature this way is obviously necessary, but a logical approach for these studies would be to determine whether the epidemiology of breast cancer in newer studies matches or differs from the published literature to date; because these new foci will likely be most fruitful if placed within the context of known risk factors for breast cancer, both to see whether markers modify those risks or are independently associated with those risk factors [11]. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial [12], although not primarily a breast cancer study, includes extensive data with which to test and develop hypotheses about breast cancer etiology. We therefore analyzed relative risk estimates for etiologic factors linked to breast cancer using the extensive questionnaire data from the approximate 75,000 post-menopausal women in the PLCO study.

## Methods

### Study population

Prorok et al. [13] previously described the full details of the PLCO trial, which includes both men and women. This analysis only includes women. The National Cancer Institute (NCI) designed this trial to determine whether routine screening with chest X-ray, flexible sigmoidoscopy, and cancer antigen 125 (CA-125) plus transvaginal ultrasound could reduce mortality from lung, colorectal, and ovarian cancers, respectively (Clinical Trials Registration: <http://www.clinicaltrials.gov>, NCT00002540). Recruitment occurred at ten U.S. screening centers (SCs) between 1993 and 2001. Women were considered eligible if they were between ages 55 and 74 and had no previous diagnosis of lung, colorectal, or ovarian cancer. Women who were receiving cancer treatment or participating in another screening or prevention trial were ineligible. Women who had bilateral oophorectomy or were taking tamoxifen were originally ineligible but later allowed to enroll. All participants provided informed consent. Institutional review boards at the NCI and each screening center approved the study. Although the current analysis does not address the PLCO trial's main objectives, the PLCO trial follows the Consolidated Standards of Reporting Trials guidelines [14].

Within-center age- and sex-stratified randomization assigned women to either a control arm, where they were asked to follow their usual medical care, or an intervention arm, where they were offered screening at regular intervals [13]. Participants completed a self-administered risk factor questionnaire at entry, which queried information on demographics, smoking, history of cancer in first-degree relatives, anthropometry, personal medical and medication use history, and personal history of cancer screening tests. Reproductive history covered menarche and menopause, parity and age at first pregnancy, and gynecologic surgeries, including hysterectomy, oophorectomy, and tubal ligation. The questionnaire ascertained age at first use and total duration of use of oral contraceptives. For menopausal hormone therapy, the question-

naire asked about ever-use, current use, and duration of use but did not differentiate estrogen-only formulations from estrogen plus progestin.

### **Cancer Ascertainment**

Participants received a mailed annual study update (ASU) around each anniversary of their randomization date. The ASUs ascertained the type and date of any cancer diagnosed in the previous year. Study staff contacted non-responding participants by mail and telephone. To validate the self-reported cancers, staff retrieved medical records (for standardized medical record abstraction of pathology reports), death certificates, data from state cancer registries, and information from next-of-kin for deceased participants.

Of 78,231 enrollees (39,116 in the control arm and 39,115 in the intervention arm), 2085 women were diagnosed with breast cancer (including 388 carcinomas in situ) through May 31, 2003. This included 121 (5.8%) self-reported (i.e., unconfirmed) and 1964 (94.2%) confirmed breast cancers. Except where noted, self-reported breast cancers from both arms were included as study endpoints for this analysis; incidence did not differ between arms (data not shown).

### **Statistical Analysis**

Analysis excluded 659 women (353 from the intervention arm and 306 from the control arm) who never returned an ASU form (and thus for whom breast cancer status was unknown) and women who reported a positive (N = 5119) or unknown (N = 1878) personal history of any cancer before randomization. We considered the 70,575 remaining women at risk for developing breast cancer from the date they completed their baseline questionnaire until the first of the following: breast cancer diagnosis, death, or last ASU.

Follow-up is scheduled for at least 13 years [15]. The mean follow-up time for all women in this analysis was 4.98 years (range, 0.01 years to 9.33 years). The mean (SD) ages at entry and exit were 62.9 years (5.4) and 67.9 years (6.1), respectively. The total number of woman-years of observation was 389,714.

Using Poisson regression in EPICURE software [16], we generated incidence rates and rate ratios (RRs) via standard likelihood ratio methods [17]. Age and calendar time were time-dependent but all other variables were time-independent. We adjusted all RRs for attained age, calendar time, PLCO screening center, age at menarche, age at natural menopause, age at first birth and parity, first-degree family history of breast cancer, benign breast disease, current height, and menopausal hormone therapy use. Complete-case analyses produced similar results

(data not shown), so, unless noted, we present analyses that included all participants. We chose the final adjustment factors by comparing models and then dropping potential confounders (e.g., education, marital status, and others) whose presence did not substantially affect the parameter estimates. The final ratio of events to independent variables was approximately 20:1. Randomization produced nearly identical distributions of demographic and reproductive characteristics between arms, and further adjustment for trial arm did not change any results (data not shown).

### **Results**

Most participants were white but nearly 7,000 (9.7%) were non-white (Table 1). More than 9,000 women (13.7%) reported having a mother, sister, or daughter with a history of breast cancer. More than 5000 women (7.3%) first gave birth after age 30. One third of the participants reported a surgical menopause, approximately one half used oral contraceptives, and two thirds used menopausal hormone therapy. Based on BMI from self-reported height and weight at baseline, one third of the population was overweight (BMI  $\geq 25$  kg/m<sup>2</sup>) and approximately one quarter was obese (BMI  $\geq 30$  kg/m<sup>2</sup>) or severely obese (BMI  $\geq 35$  kg/m<sup>2</sup>).

As expected, age-specific breast cancer incidence rates rose with increasing age (Table 2). Compared with white women, African-American and Asian/Pacific Islander women were non-significantly more likely to develop breast cancer after adjustment for other factors (see table footnote). Increasing parity and earlier age at first birth were inversely associated with breast cancer. Later ages at menarche and natural menopause were inversely and positively, respectively, associated with breast cancer. Current menopausal hormone therapy use at baseline, regardless of duration, significantly increased risk, but the baseline questionnaire did not query hormone therapy formulation or regimen. Height, weight, and BMI were positively associated with breast cancer, although weight and BMI associations emerged only after statistical adjustment and only a few categories produced statistically significant associations.

### **Discussion**

Our analysis of postmenopausal breast cancer in the PLCO study revealed interesting differences from the generally established epidemiology of breast cancer. Increasing age, parity, family history of breast cancer, and use of menopausal hormone therapy were all associated with breast cancer as expected. Associations with other key risk factors – age at menarche, age at menopause, and obesity – were slightly different from the previously published literature. These differences have at least two implications for ongoing and future research on breast cancer.

**Table 1: Baseline characteristics for 70,575 women in the PLCO Cancer Screening Trial Cohort.**

	Number	%
Age at baseline		
55–59	24,381	34.6
60–64	21,405	30.3
65–69	15,405	21.8
70–74	9,384	13.3
Race/ethnicity		
White	62,425	88.5
African-American	4,063	5.8
Asian/Pacific Islander	2,754	3.9
Other*	1,333	1.9
Education		
Less than H.S.	4,598	6.5
Completed H.S.	28,588	40.5
Beyond H.S.	37,215	52.7
Unknown	174	0.3
Marital status		
Married or living as married	48,749	69.1
Widowed	9,700	13.7
Divorced or separated	9,616	12.7
Never married/missing	2,510	4.5
Mother or sister with breast cancer		
No	57,214	81.1
Yes	9,692	13.7
Unknown	3,669	5.2
Age at menarche		
< 12	14,259	20.2
12 – 13	37,816	53.6
14 – 15	15,105	21.4
≥ 16	3,208	4.6
Missing	187	0.3
Years of oral contraceptive use		
None	32,170	45.6
< 1 year	10,219	14.5
2 – 3 years	7,636	10.8
4 – 5 years	5,208	7.4
6 – 9 years	6,303	8.9
≥ 10 years	8,830	12.5
Missing	209	0.3
Parity and age at first birth		
Nulliparous	6,454	9.1
1–2		
< 20 years	2,499	3.5
20–24 years	9,336	13.2
25–29 years	6,629	9.4
30–34 years	2,405	3.4
≥ 35 years	1,021	1.5
3–4		
< 20 years	5,721	8.1
20–24 years	16,227	23.0
25–29 years	5,942	8.4
30–34 years	1,020	1.5
≥ 35 years	343	0.5
≥ 5		
< 20 years	3,818	5.4
20–24 years	7,162	10.2
25–29 years	1,506	2.1
30–34 years	193	0.3
≥ 35 years	194	0.3
Missing or unknown	105	0.2

**Table 1: Baseline characteristics for 70,575 women in the PLCO Cancer Screening Trial Cohort. (Continued)**

Menopause Type		
Natural	43,572	61.7
Surgical	23,312	33.3
Radiation or medications	2,346	3.3
Missing	1,345	41.9
Age at Natural Menopause		
< 45 years	4,468	6.3
45–49 years	11,175	15.8
50–54 years	22,134	31.4
55+ years	5,709	8.1
Missing	86	0.1
Menopausal hormone therapy use		
None	23,262	33.0
Former use	11,435	16.2
Current use, ≤ 5 years	11,546	16.4
Current use, > 5 years	23,712	33.6
Missing	620	0.9
Body Mass Index (BMI; kg/m <sup>2</sup> )		
< 18.5	892	1.3
18.5 – 24.9	27,251	38.6
25 – 29	24,214	34.3
30 – 34.9	11,102	15.7
≥ 35	6,297	8.9
Missing	819	1.2

\*Other race/ethnicity includes Hispanic, American Indian, and missing/unknown.

First, the magnitude of some risk factor associations may be changing. Published studies have reported consistent, linear risk relationships with older ages at menarche (e.g.: 5% decrease in risk per 1-year delay after age 12) and menopause (e.g.: 3% increase in risk per 1-year delay age at menopause)[8,9,18]. In contrast, we observed a fairly uniform decreased risk with older ages at menarche and a non-significant increased risk only in the oldest age-at-menopause group. The larger numbers of older women in the PLCO cohort could explain the lower RRs. Alternatively, inaccurate recall, especially among older women [19], or non-differential misclassification could be a factor, because our questionnaire collected only categorical data on these ages.

Body size is positively associated with postmenopausal breast cancer [20]. In a pooled analysis of cohort studies, risk increased significantly by 7% per 4-kg/m<sup>2</sup> BMI increase, 7% per 5-cm height increase, and 6% per 10-kg weight increase [7]. In our analysis, all three factors increased the relative risks by 20%. Despite the large sample size, only the RRs for the highest categories were statistically significant; the BMI association was stronger than the height and weight associations.

We observed a higher RR for breast cancer for the combination of low parity and later age at first birth, whereas an earlier meta-analysis reported declining RRs with lower parity in women whose first birth occurred at older ages

**Table 2: Number of breast cancers, person-years, rates, and RRs by demographic, reproductive, and anthropometric factors.**

	Breast Cancers*	Woman-Years	Crude Rate	RR**	95% CI
<b>Attained Age</b>					
55–59	274	63,088	434.31	1.00	Ref.
60–64	608	108,640	559.65	1.36	1.18–1.57
65–69	582	104,433	557.30	1.44	1.24–1.67
70–74	434	79,134	548.44	1.48	1.26–1.73
75+	187	34,419	543.30	1.47	1.21–1.79
<b>Race</b>					
White	1,854	345,926	535.95	1.00	Ref.
African-American	89	19,765	450.29	1.05	0.84–1.32
Asian/Pacific Islander	111	17,230	644.23	1.14	0.86–1.51
Other/unknown	31	6,793	456.35	0.92	0.64–1.32
<b>Family history of breast cancer</b>					
No	1696	336,410	504.15	1.00	Ref.
Yes	389	53,304	729.78	1.44	1.29–1.60
<b>Number of Live Births</b>					
0	240	35,545	675.20	1.00	Ref.
1	160	28,296	565.45	0.70	0.55–0.89
2	524	88,510	592.02	0.76	0.62–0.92
3	526	96,163	546.99	0.75	0.62–0.91
4	331	66,673	496.45	0.72	0.59–0.88
5+	301	73,888	407.37	0.65	0.53–0.80
<b>Age at First Birth</b>					
None	240	35,545	675.20	1.00	Ref.
< 20	267	62,165	429.50	0.68	0.53–0.86
20–24	901	181,709	495.85	0.74	0.59–0.91
25–29	471	80,523	584.93	0.83	0.66–1.03
30–34	148	20,822	710.79	1.03	0.81–1.31
35+	47	6,894	681.75	1.02	0.74–1.41
<b>Age at Menarche</b>					
< 12 years	457	76,987	593.61	1.00	Ref.
12–13 years	1099	209,082	525.63	0.86	0.77–0.97
14–15 years	439	84,595	518.94	0.85	0.74–0.97
≥ 16 years	88	17,874	492.34	0.81	0.65–1.02
<b>Age at Menopause</b>					
< 45 years	123	25,254	487.05	1.00	Ref.
45–49 years	340	64,113	530.31	1.07	0.87–1.31
50–54 years	700	126,080	555.20	1.12	0.92–1.35
55+ years	211	32,192	655.44	1.29	1.03–1.62
Surgical menopause	574	122,386	469.01	0.84	0.69–1.02
Radiation/medication	94	12,061	779.37	1.32	1.01–1.74
<b>Menopausal hormone therapy use</b>					
Never	571	134,329	425.08	1.00	Ref.
Former	280	64,773	432.28	1.02	0.88–1.18
Current, < 5 years	372	61,931	600.67	1.44	1.26–1.66
Current, ≥ 5 years	847	125,006	677.57	1.67	1.49–1.87
<b>Weight (kg)</b>					
< 60	437	82,961	526.75	1.00	Ref.
60 – 64.9	310	59,068	524.82	1.03	0.86–1.19
65 – 69.9	311	56,091	554.46	1.18	0.97–1.30
70 – 74.9	257	49,325	521.03	1.08	0.92–1.26
75 – 79.9	267	47,072	567.22	1.21	1.03–1.42
≥ 80	486	91,892	528.88	1.20	1.04–1.38
<b>Height (m)</b>					
< 1.60	527	101,460	519.42	1.00	Ref.
1.60 – 1.64	605	117,236	516.05	1.01	0.89–1.13
1.65 – 1.69	561	102,205	548.90	1.06	0.94–1.20
≥ 1.70	385	66,707	577.15	1.11	0.97–1.27
<b>BMI (kg/m<sup>2</sup>)</b>					
< 18.5	25	5,135	486.85	0.88	0.59–1.32
18.5 – 24.9	848	154,447	549.06	1.00	Ref.

**Table 2: Number of breast cancers, person-years, rates, and RRs by demographic, reproductive, and anthropometric factors. (Continued)**

25 – 29	712	133,799	532.14	1.06	0.95–1.17
30 – 34.9	305	59,109	516.00	1.10	0.97–1.26
≥ 35	173	32,478	532.67	1.21	1.02–1.43

\* Includes confirmed invasive cancers, confirmed in situ lesions, and self-reported cancers.

\*\* Adjusted for attained age, screening center, age at menarche, age at menopause, family history of breast cancer, benign breast disease, height, and menopausal hormone therapy (all in categories as shown in the table), plus combined age at first birth and parity (nulliparous or first birth after 35 years, first birth before age 25, first birth 25–34 years, or unknown) and calendar time (5/31/1993 – 5/31/1995, 6/1/1995 – 5/31/1997, 6/1/1997 – 5/31/1999, 6/1/1999 – 5/31/2001, and 6/1/2001 – 5/31/2003). RRs for age at first birth and parity were adjusted for the other factor.

Not shown are unknown parity (3 breast cancers and 638 person-years), age at first birth (11 breast cancers and 2,635 person-years), age at menarche (2 breast cancers and 1,177 person-years), age at or type of menopause (43 breast cancers and 7,628 person-years), menopausal hormone therapy use (15 breast cancers and 3,676 person-years), weight (17 breast cancers and 3,304 person-years), height (7 breast cancers and 2,107 person-years), and BMI (22 breast cancers and 4,747 person-years).

[21]. Both that and our study included few multiparous women who first gave birth after age 35.

These changes could reflect underlying demographic changes. Mean age of menarche among U.S. females has declined in recent decades, whereas later age at natural menopause is more common than before [22,23]. The prevalence of women who first give birth after age 35 is increasing, as is the prevalence of obesity [24]. These factors are potentially related: obesity might spark early estrogen production and the onset of puberty, whereas parity and BMI are also associated with later age at menopause [25-28]. Teasing apart the quantitative effect of these changes on risk factor associations, as well as the underlying biologic implications, may prove to be a challenge.

Changing distributions of risk factors will affect the use of risk prediction models that project individual probabilities of breast cancer and influence eligibility for clinical trials. The widely used Gail model [29] relies on readily available medical information, such as age at first birth and age at menopause. Modified prediction models incorporate additional clinical information, such as breast density [30]. If the relative risk measures that underlie the projection of absolute risks in these models are changing, then there is the potential for the models to lose some of their current calibratory and discriminatory ability. Continued assessment of model performance among newer population-based studies with diverse populations could address this and shed further light on the potential influence of changing demographics on the epidemiology of postmenopausal breast cancer.

The known risk factors for breast cancer account for perhaps only 50% of the population burden of breast cancer [31]. A polygenic model of breast cancer hypothesizes that many genetic factors contribute individually small but collectively large effects that could explain the remaining 50% of the population attributable risk [32]. Based on extensive results to date of candidate pathways, the overall effect of low-penetrance SNPs is minimal [33]. The SNP-based associations that have emerged from marker-based

scans have unknown function or functions unrelated to the hormonal pathways linked with breast cancer [34,35]. Other important genetic markers with relevant functions might surface. Exploration of genetic factors is likely to be most fruitful if placed within the context of the known risk factors for breast cancer, both to see whether markers modify those risks or are independently associated with those risk factors [11].

Whether known or future genetic markers can improve the performance of existing risk prediction models – or potential new models that incorporate the clinical heterogeneity of breast cancers [36]–is uncertain. Readily available lifestyle or questionnaire-based information, such as reproductive history, will remain the cornerstone of risk prediction and stratification even if it becomes easy, inexpensive, and risk-free for large numbers of women to determine their genetic profile because the small-magnitude risk associations are unlikely to be useful for prediction [37,38]. Changes in the underlying associations between those risk factors and breast cancer would not adversely affect such evaluation, but it would require continued surveillance of breast cancer epidemiology among contemporary populations, such as PLCO, both individually and within large-scale replication efforts [32].

Our large sample size makes it unlikely that the deviations from expectation that we observed were due to chance. Overall exposure and endpoint data were likely good, but residual confounding might exist. The questionnaire lacked information on some risk factors, such as breastfeeding [8], physical activity [39], and alcohol use [40]. For others – particularly menopausal hormone therapy [41] – the baseline questionnaire did not allow us to differentiate the higher-risk estrogen-plus-progestin formulations from estrogen-only formulations. Compared with 2001 U.S. Census Bureau data on women aged 55–74 [42], lower percentages of PLCO participants reported receiving some formal education beyond high school across all racial/ethnic groups: 58% vs. 53% for whites, 67% vs. 52% for African-Americans, and 57% vs. 52% for Asian/Pacific Islanders. We cannot rule out that other unmeasured factors may make our study population

slightly different from the U.S. population on the whole. Our analysis covered a relatively short follow-up, and continued follow-up of the PLCO population may confirm both the validity and generalizability of our findings.

## Conclusion

In conclusion, this study of over 75,000 post-menopausal women suggests that population-level and demographic changes might influence the magnitude of well-established associations between certain recognized risk factors and breast cancer. These potential changes may become increasingly important as new molecular epidemiologic efforts attempt to expand upon existing methods for understanding relative and absolute risks for breast cancer.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

JVL and PH designed the investigation. JVL analyzed the data. JVL, ARK, SSB, PMM, SCC, MFL, RNH, PCP, CDB and PH interpreted the results. JVL, ARK, SSB, CDB, and PD drafted the manuscript, and JVL, ARK, SSB, PMM, SCC, MFL, RNH, PCP, CDB, and PH edited the manuscript.

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