Associations of oral contraceptives with mammographic breast density

Carmen Smotherman[1], Rulla Tamimi[2], John Heine[3], Graham Colditz[4,5], Bernard Rosner[2], Lusine Yaghjyan[1]

[1]University of Florida, College of Public Health and Health Professions and College of Medicine, Department of Epidemiology, Gainesville, FL, USA;[2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA;[3]Cancer Epidemiology Department, Moffitt Cancer Center & Research Institute, Tampa, FL;[4]Washington University in St. Louis School of Medicine, Department of Surgery, St. Louis, MO, USA;[5]Institute for Public Health, Washington University in St. Louis, St. Louis, MO, USA

Background

- High mammographic breast density is a well-established and strong breast cancer risk factor

- The majority of the studies have found a positive association between oral contraceptives (OC) use and subsequent breast cancer

  - more evident among current/recent OC users relative to past or non-users

  - greater risk among high-dose estrogen OC users

- OCs can potentially increase breast density by inducing epithelial proliferation and thus increasing the area of the breast occupied by fibroglandular tissue

- The evidence on the possible association between OC use and mammographic breast density is extremely limited

Objectives

- We investigated the associations of oral contraceptive (OC) use with percent breast density (PD), absolute dense area (DA), non-dense area (NDA), and a novel image intensity variation (V) measure in premenopausal women

Study Design/Methods

- Cancer-free women from a nested case-control study within Nurses' Health Study II cohort

  - 25-42 years old at enrollment

  - Matching on age at the time of blood collection, menopausal status and postmenopausal hormone use (current vs. not current) at blood draw, day/time of blood draw, race/ethnicity and day in the luteal phase

- Additional eligible women within this cohort (without a history of any cancer other than non-melanoma skin) who were not included in the original nested breast cancer case-control study

Oral Contraceptives Use
- Information on OC use was collected in 1989 and then updated biennially.

- OC use was defined from the questionnaire closest to the mammogram date

- Exposure categorization approaches:

  - OC use status (never, past, and current)
  - Age at first use
  - Age at last use
  - Total duration of OC use (in years)
  - Duration since last use (in months)

Table 1. Characteristics of premenopausal women by OC use status

Characteristic	Oral contraceptive use		
	Never (n=184)	Past (n=952)	Current (n=97)
Mean (SD)			
Percent density	39.67 (18.06)	40.52 (17.75)	40.55 (16.91)
Absolute dense area	42.94 (24.17)	44.47 (24.03)	40.26 (18.73)
V-measure	324.9 (135.5)	341.1 (127.5)	330.6 (132.8)
Non-dense area	73.89 (46.87)	73.34 (45.47)	61.98 (29.39)
Age at mammogram, years[a]	44.33 (4.35)	44.95 (4.14)	43.40 (4.63)
Age at menarche	12.27 (1.50)	12.48 (1.44)	12.17 (1.48)
Age at first child's birth, years	26.57 (4.61)	26.64 (4.62)	27.14 (4.69)
Body Mass Index, kg/m^2	26.00 (6.16)	25.86 (5.78)	24.93 (4.81)
Alcohol use, g/day	3.246 (5.610)	4.306 (7.428)	4.972 (6.556)
Percentages			
Nulliparous	23	15	24
Parous with age at first birth <25 years	28	28	24
Parous with age at first birth ≥25 years	48	56	51
Family history of breast cancer (yes)	11	9	8
Biopsy-confirmed benign breast disease	20	17	14

[a]No age adjustment

Table 2. Associations of oral contraceptive use with breast density measures (β and 95%CI)[a]

Oral contraceptive use	Breast density measures			
	Percent density[b]	Absolute dense area[b]	Non-dense area[b]	V-measure
OC status				
n	1,233	1,233	1,233	1,105
Never	0	0	0	0
Past	0.10 (-0.09;0.29)	0.13 (-0.12;0.39)	-0.01 (-0.28;0.25)	22.12 (0.24;44.00)
Current	-0.06 (-0.37;0.24)	-0.20 (-0.59;0.18)	-0.19 (-0.56;0.18)	11.25 (-21.78;44.27)
p-trend[c]	0.99	0.66	0.43	0.27
Age at first OC use				
n	1,025	1,025	1,025	923
Never	0	0	0	0
<20	0.11 (-0.10;0.32)	0.13 (-0.16;0.41)	-0.02 (-0.31;0.27)	26.88 (3.18;50.58)
20-24	0.07 (-0.14;0.28)	0.10 (-0.18;0.38)	-0.04 (-0.32;0.24)	20.23 (-4.24;44.71)
25-29	-0.08 (-0.42;0.26)	-0.05 (-0.49;0.39)	-0.07 (-0.40;0.54)	2.61 (-29.00;34.23)
≥30	-0.00 (-0.33;0.33)	-0.16 (-0.63;0.31)	-0.15 (-0.61;0.32)	0.28 (-34.16;34.72)
p-trend[c]	0.25	0.16	0.84	0.03
Total duration of use, in years				
n	1,216	1,216	1,216	1,092
Never	0	0	0	0
≤ 1	0.11 (-0.14;0.37)	0.15 (-0.18;0.48)	0.01 (-0.34;0.36)	19.45 (-6.89;45.78)
1-<2	-0.04 (-0.39;0.32)	-0.07 (-0.55;0.41)	0.08 (-0.43;0.60)	43.61 (5.31;81.91)
2-<5	0.08 (-0.14;030)	0.17 (-0.11;0.46)	0.06 (-0.24;0.36)	17.91 (-6.85;42.67)
5-<10	0.15 (-0.08;0.38)	0.06 (-0.25;0.37)	-0.29 (-0.58;0.00)	22.56 (-2.48;47.60)
≥10	-0.06 (-0.31;0.19)	-0.05 (-0.39;0.29)	0.10 (-0.23;0.44)	16.44 (-12.89;45.77)
p-trend[c]	0.69	0.44	0.59	0.58
Time since last use, in months[d]				
n	949	949	949	848
Never	0	0	0	0
1-23	0.08 (-0.22;0.39)	0.08 (-0.36;0.51)	-0.06 (-0.48;0.37)	26.14 (-8.78;61.06)
24-47	0.31 (-0.03;0.65)	0.41 (-0.08;0.91)	-0.25 (-0.69;0.19)	47.58 (8.04;87.11)
48-71	0.27 (-0.07;0.62)	0.33 (-0.22;0.88)	-0.14 (-0.64;0.36)	14.28 (-23.49;52.05)
72-95	0.02 (-0.35;0.39)	0.20 (-0.32;0.73)	0.23 (-0.31;0.76)	38.43 (2.20;74.67)
96-119	-0.14 (-0.54;0.26)	-0.15 (-0.79;0.49)	0.04 (-0.46;0.53)	15.76 (-27.92;59.45)
120+	0.10 (-0.10;0.30)	0.11 (-0.16;0.38)	-0.01 (-0.29;0.26)	17.87 (-4.84;40.57)
p-trend[c]	0.42	0.37	0.47	0.16
Age at last use, continuous years[d]				
n	922	922	922	827
	0.00 (-0.01;0.01)	0.00 (-0.01;0.02)	0.00 (-0.01;0.01)	0.53 (-0.56;1.62)

[a]Adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, >13), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), alcohol use (none, >0-<5, ≥5 g/day), and parity and age at first child's birth (nulliparous, parous with age at first birth <25, parous with age at first birth ≥25;[b]Square-root transformed;[c]Does not include never users;[d]Among past users

Methods (continued)

Mammographic Breast Density
- PD, DA, and NDA were measured from digitized film mammograms using a computer-assisted thresholding technique

- V measure was obtained from mammographic images with a previously developed algorithm that measures the standard deviation of pixel values in the eroded breast region.

Statistical Analyses
- Generalized linear regression (square root-transformed PD, DA, and NDA, and untransformed V)

- The magnitude of the associations was described using the regression coefficients (β), along with their 95% confidence intervals [CI]

- The regression estimates were adjusted for known breast cancer risk factors

Covariates
- Age, BMI, age at menarche, parity/age at first child's birth, menopausal status/hormone use, family history of breast cancer, alcohol use, a history of benign breast disease are available from biannual questionnaires, at the time of mammogram

Results

- No association between OC use status and PD, DA, and NDA (Table 2)

- Higher V measure in past as compared to never users (β=22.12, 95% CI 0.24,44.00) (Table 2)

- Inverse association between age at first OC use and the V measure:

  - <20 years vs. never: β=26.88, 95% CI -3.18,50.58
  - 20-24 years vs. never: β=20.23, 95% CI -4.24,44.71
  - 25-29 years vs. never: β=2.61, 95% CI -29.00,34.23
  - ≥30 years vs. never: β=0.28, 95% CI -34.16,34.72, p-trend=0.03) (Table 2)

- No other significant associations for any of the other OC variables with any of the density measures (Table 2)

Conclusions

- While we found no associations of OC with breast density (PD), absolute dense area (DA), non-dense area (NDA), we observed a suggestive positive association of past use and an inverse association of age at first use with the V measure that warrant further investigation.