|  |
| --- |
| **Table S1. Association between epidemiologic characteristics and high CA72.4 by menopausal status at blood collection in healthy women: EPIC** |
|  | **Premenopausal** |  | **Postmenopausal** |
|  | **Low\*N=151N (%)** | **High\*N=24N (%)** | **Crude OR (95% CI)** | **p** |   | **Low\*N=457N (%)** | **High\*N=81N (%)** | **Crude OR (95% CI)** | **p** |
|  |  |  |  |  |  |  |  |  |  |
| **Age at blood draw** |  |  |  |  |  |  |  |  |  |
|  ≤40 | 28 (19) | 5 (21) | 1.00 (ref) |  |  |  |  |  |  |
|  >40 | 123 (81) | 19 (79) | 0.87 (0.30, 2.52) | 0.79 |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  ≤60 |  |  |  |  |  | 217 (47) | 42 (52) | 1.00 (ref) |  |
|  >60 |  |  |  |  |  | 240 (53) | 39 (48) | 0.84 (0.52, 1.35) | 0.47 |
|  |  |  |  |  |  |  |  |  |  |
| **Oral contraceptive use** |  |  |  |  |  |  |  |  |  |
|  Never | 40 (27) | 8 (36) | 1.00 (ref) |  |  | 251 (57) | 50 (63) | 1.00 (ref) |  |
|  Ever | 108 (73) | 14 (64) | 0.65 (0.25, 1.66) | 0.37 |  | 193 (43) | 29 (37) | 0.75 (0.46, 1.24) | 0.26 |
|  |  |  |  |  |  |  |  |  |  |
|  Never | 40 (28) | 8 (40) | 1.00 (ref) |  |  | 251 (59) | 50 (67) | 1.00 (ref) |  |
|  ≥5 years | 58 (40) | 8 (40) | 0.69 (0.24, 1.99) | 0.49 |  | 86 (20) | 9 (12) | 0.53 (0.25, 1.11) | 0.09 |
|  >5 years | 47 (32) | 4 (20) | 0.43 (0.12, 1.52) | 0.19 |  | 92 (21) | 16 (21) | 0.87 (0.47, 1.61) | 0.66 |
|  |  |  |  |  |  |  |  |  |  |
| **Parity** |  |  |  |  |  |  |  |  |  |
|  Nulliparous | 14 (10) | 4 (20) | 1.00 (ref) |  |  | 54 (13) | 8 (11) | 1.00 (ref) |  |
|  Parous | 132 (90) | 16 (80) | 0.42 (0.12, 1.45) | 0.17 |  | 375 (87) | 62 (89) | 1.12 (0.51, 2.46) | 0.79 |
|  |  |  |  |  |  |  |  |  |  |
|  0 | 14 (10) | 4 (20) | 1.00 (ref) |  |  | 54 (13) | 8 (12) | 1.00 (ref) |  |
|  1-2 | 82 (61) | 10 (50) | 0.43 (0.12, 1.55) | 0.20 |  | 224 (54) | 35 (51) | 1.06 (0.46, 2.40) | 0.90 |
|  >2 | 38 (28) | 6 (30) | 0.55 (0.14, 2.25) | 0.41 |  | 138 (33) | 26 (38) | 1.27 (0.54, 2.98) | 0.58 |
|  |  |  |  |  |  |  |  |  |  |
| **Uniliateral oophorectomy** |  |  |  |  |  |  |  |  |  |
|  No | 150 (99) | 23 (96) | 1.00 (ref) |  |  | 442 (97) | 77 (95) | 1.00 (ref) |  |
|  Yes | 1 (1) | 1 (4) | 6.52 (0.39, 107.9) | 0.19 |  | 15 (3) | 4 (5) | 1.53 (0.50, 4.74) | 0.46 |
|  |  |  |  |  |  |  |  |  |  |
| **Hysterectomy** |  |  |  |  |  |  |  |  |  |
|  No | 134 (98) | 20 (100) |  -- |  |  | 313 (85) | 51 (91) | 1.00 (ref) |  |
|  Yes | 3 (2) | 0 (0) |  -- |  -- |  | 55 (15) | 5 (9) | 0.56 (0.21, 1.46) | 0.23 |
|  |  |  |  |  |  |  |  |  |  |
| **Age at menopause** |  |  |  |  |  |  |  |  |  |
|  <= 47 years |  |  |  |  |  | 114 (32) | 17 (27) | 1.00 (ref) |  |
|  48 - 51 years |  |  |  |  |  | 130 (37) | 28 (44) | 1.44 (0.75, 2.78) | 0.27 |
|  > 51 years |  |  |  |  |  | 112 (31) | 18 (29) | 1.08 (0.53, 2.20) | 0.84 |
|  |  |  |  |  |  |  |  |  |  |
| **Hormone Replacement Therapy**  |  |  |  |  |  |  |  |  |
|  Never used HRT |  |  |  |  |  | 307 (67) | 50 (62) | 1.00 (ref) |  |
|  Ever used HRT |  |  |  |  |  | 150 (33) | 31 (38) | 1.27 (0.78, 2.07) | 0.34 |
|  |  |  |  |  |  |  |  |  |  |
| **Ovulatory cycles¶** |  |  |  |  |  |  |  |  |  |
|  ≤ 368 | 42 (44) | 7 (64) | 1.00 (ref) |  |  |  |  |  |  |
|  > 368 | 53 (56) | 4 (36) | 0.45 (0.12, 1.65) | 0.23 |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  ≤ 368 |  |  |  |  |  | 78 (22) | 10 (18) | 1.00 (ref) |  |
|  369-414 |  |  |  |  |  | 81 (23) | 12 (22) | 1.16 (0.47, 2.83) | 0.75 |
|  415-450 |  |  |  |  |  | 94 (26) | 16 (29) | 1.33 (0.57, 3.09) | 0.51 |
|  > 450 |  |  |  |  |  | 105 (29) | 17 (31) | 1.26 (0.55, 2.91) | 0.58 |
|  |  |  |  |  |  |  |  |  |  |
| **BMI (kg/m2)** |  |  |  |  |  |  |  |  |  |
|  <25 | 85 (66) | 10 (43) | 1.00 (ref) |  |  | 193 (44) | 38 (51) | 1.00 (ref) |  |
|  ≥25 | 44 (34) | 13 (57) | 2.51 (1.02, 6.18) | 0.05 |  | 241 (56) | 37 (49) | 0.78 (0.48, 1.27) | 0.32 |
|  |  |  |  |  |  |  |  |  |  |
| **Smoking** |  |  |  |  |  |  |  |  |  |
|  Never | 80 (54) | 17 (71) | 1.00 (ref) |  |  | 270 (60) | 49 (61) | 1.00 (ref) |  |
|  Former | 36 (24) | 3 (13) | 0.39 (0.11, 1.42) | 0.15 |  | 99 (22) | 9 (11) | 0.50 (0.24, 1.06) | 0.07 |
|  Current | 33 (22) | 4 (17) | 0.57 (0.18, 1.82) | 0.34 |  | 80 (18) | 22 (28) | 1.52 (0.86, 2.66) | 0.15 |
|   |   |   |   |   |   |   |   |   |   |
| \*Low < 1.119 U/mL; High >1.119 U/mL¶time between menarche and menopause with time subtracted for oral contraceptive use, pregnancy and breastfeeding**;** categories based on quartile cutpoints; ‡CA72.4 is elevated (>1.119) in 13% of premenopausal controls and 15% of postmenopausal controls, p = 0.46 |

|  |
| --- |
| **Table S2. Multivariate adjusted association between epidemiologic characteristics and CA125 and CA15.3 by menopausal status at blood collection in healthy women: EPIC\*** |
|  | **PREMENOPAUSAL** |  | **POSTMENOPAUSAL** |
|  |  | **CA125 (U/mL)** | **CA15.3 (mU/mL)** | **HE4 (pM)** |  |  | **CA125 (U/mL)** | **CA15.3 (U/mL)** | **HE4 (pM)** |
|  | **N\* (%)** | **Mean (95% CI)†** | **Mean (95% CI)†** | **N\* (%)** | **Mean (95% CI)†** |  | **N\* (%)** | **Mean (95% CI)†** | **Mean (95% CI)**† | **N\* (%)** | **Mean (95% CI)†** |
| **Menopausal status‡** | 485 (26) | 28.1 (26.1, 30.3) | 566.8 (529.2, 607.0) | 175 (25) | 19.1 (17.3, 21.1) |  | 1417 (24) | 17.9 (17.3, 18.6) | 612.4 (592.8, 632.7) | 538 (75) | 18.8 (18.0, 19.6) |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Age at blood draw** |  |  |  |  |  |  |  |  |  |  |  |
|  < 41 | 75 (15) | 27.1 (23.0, 31.9) | 600.7 (522.7, 690.3) | 33 (19) | 18.1 (14.8, 22.3) |  | 0 (0) | -- | -- | 0 (0) | -- |
|  41-50 | 269 (55) | 29.3 (27.1, 31.7) | 557.9 (521.6, 596.8) | 103 (59) | 17.0 (15.5, 18.6) |  | 47 (3) | 18.9 (16.0, 22.4) | 542.7 (462.1, 637.5) | 9 (2) | 16.4 (12.1, 22.3) |
|  51-60 | 141 (29) | 24.8 (21.9, 28.1) | 529.8 (475.8, 589.9) | 39 (22) | 14.3 (12.0, 17.1) |  | 697 (49) | 17.9 (17.2, 18.7) | 632.2 (606.0, 659.5) | 250 (46) | 18.6 (17.5, 19.7) |
|  61-70 | 0 (0) | -- | -- | 0 (0) | -- |  | 586 (41) | 17.8 (16.9, 18.6) | 611.2 (583.8, 639.8) | 227 (42) | 19.8 (18.6, 21.1) |
|  > 70 | 0 (0) | -- | -- | 0 (0) | -- |  | 87 (6) | 20.9 (18.3, 23.9) | 572.8 (504.1, 650.8) | 52 (10) | 25.9 (22.3, 30.0) |
|  ptrend |  | 0.36 | 0.20 |  | 0.11 |  |  | 0.44 | 0.49 |  | **0.0003** |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Age at menarche** |  |  |  |  |  |  |  |  |  |  |  |
|  < 12 | 93 (20) | 27.8 (24.4, 31.7) | 542.1 (485.4, 605.4) | 33 (20) | 15.8 (13.5, 18.6) |  | 171 (13) | 17.9 (16.4, 19.5) | 622.5 (572.4, 676.9) | 63 (12) | 20.1 (17.9, 22.6) |
|  12 | 94 (20) | 27.7 (24.3, 31.6) | 574.3 (514.7, 640.9) | 33 (20) | 17.4 (14.9, 20.3) |  | 257 (19) | 18.0 (16.8, 19.3) | 593.2 (555.2, 633.8) | 102 (20) | 19.7 (18.0, 21.5) |
|  13 | 118 (26) | 26.4 (23.5, 29.6) | 559.6 (508.6, 615.9) | 48 (29) | 16.8 (14.8, 19.2) |  | 301 (22) | 17.8 (16.7, 19.0) | 629.4 (591.8, 669.4) | 117 (23) | 19.5 (18.0, 21.2) |
|  14 | 94 (20) | 28.1 (24.7, 32.1) | 510.4 (457.2, 569.7) | 34 (20) | 16.5 (14.1, 19.2) |  | 336 (25) | 18.6 (17.5, 19.8) | 617.0 (582.4, 653.7) | 129 (25) | 18.7 (17.3, 20.2) |
|  > 14 | 60 (13) | 27.2 (23.1, 32.0) | 586.6 (511.2, 673.2) | 20 (12) | 15.9 (12.7, 19.9) |  | 300 (22) | 17.8 (16.7, 19.0) | 600.0 (563.8, 638.5) | 104 (20) | 20.3 (18.7, 22.2) |
|  ptrend |  | 0.92 | 0.99 |  | 0.97 |  |  | 0.86 | 0.82 |  | 0.92 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Oral contraceptive use** |  |  |  |  |  |  |  |  |  |  |
|  Never | 145 (31) | 27.9 (24.9, 31.2) | 509.3 (463.8, 559.2) | 48 (28) | 15.7 (13.6, 18.1) |  | 776 (56) | 18.3 (17.5, 19.1) | 626.9 (602.2, 652.7) | 301 (58) | 20.0 (19.0, 21.1) |
|  Ever | 320 (69) | 27.4 (25.5, 29.4) | 571.6 (538.6, 606.5) | 122 (72) | 16.9 (15.6, 18.3) |  | 604 (44) | 17.9 (17.0, 18.8) | 597.6 (570.5, 626.1) | 222 (42) | 19.0 (17.9, 20.3) |
| pdiff |  | 0.81 | 0.06 |  | 0.41 |  |  | 0.54 | 0.15 |  | 0.26 |
|  >= 2 years | 101 (22) | 27.3 (24.1, 31.1) | 596.8 (536.1, 664.3) | 44 (27) | 16.9 (14.7, 19.5) |  | 153 (12) | 18.8 (17.2, 20.6) | 607.5 (556.7, 662.9) | 51 (10) | 20.7 (18.3, 23.5) |
|  > 2 - 5 years | 68 (15) | 30.0 (25.8, 34.9) | 527.7 (464.8, 599.1) | 22 (13) | 17.9 (14.9, 21.6) |  | 111 (8) | 18.0 (16.2, 20.0) | 574.3 (518.7, 635.8) | 44 (9) | 17.6 (15.4, 20.1) |
|  > 5 - 10 years | 77 (17) | 26.0 (22.5, 30.1) | 571.1 (506.4, 644.1) | 27 (16) | 19.5 (16.4, 23.2) |  | 127 (10) | 17.0 (15.4, 18.8) | 598.4 (543.4, 658.9) | 46 (9) | 20.8 (18.1, 23.8) |
|  > 10 years | 62 (14) | 26.7 (22.3, 32.0) | 617.1 (531.4, 716.5) | 24 (15) | 14.8 (11.8, 18.6) |  | 161 (12) | 17.9 (16.3, 19.6) | 616.1 (564.2, 672.8) | 62 (12) | 16.7 (14.8, 18.9) |
|  ptrend |  | 0.57 | 0.13 |  | 0.56 |  |  | 0.56 | 0.86 |  | **0.01** |
|  ptrend§ |  | 0.71 | 0.18 |  | 0.36 |  |  | 0.78 | 0.52 |  | **0.03** |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Parity** |  |  |  |  |  |  |  |  |  |  |  |
|  Nulliparous | 48 (11) | 29.9 (24.9, 35.8) | 576.8 (495.6, 671.3) | 18 (11) | 14.4 (11.6, 17.8) |  | 152 (12) | 16.5 (15.1, 18.1) | 607.0 (557.2, 661.2) | 62 (12) | 21.5 (19.3, 24.0) |
|  Parous | 406 (89) | 27.4 (25.8, 29.1) | 548.4 (521.8, 576.4) | 148 (89) | 16.8 (15.7, 18.0) |  | 1163 (88) | 18.2 (17.6, 18.8) | 611.0 (592.5, 630.0) | 437 (88) | 19.3 (18.5, 20.1) |
| pdiff |  | 0.39 | 0.54 |  | 0.18 |  |  | 0.06 | 0.89 |  | 0.07 |
|  1 child | 74 (17) | 28.2 (24.3, 32.7) | 509.8 (452.0, 575.1) | 23 (15) | 15.8 (13.2, 18.9) |  | 200 (15) | 17.3 (16.0, 18.8) | 602.8 (558.7, 650.3) | 84 (17) | 19.6 (17.8, 21.5) |
|  2 children | 215 (50) | 27.6 (25.3, 30.0) | 557.7 (520.1, 598.1) | 69 (45) | 15.4 (13.8, 17.1) |  | 513 (40) | 18.2 (17.3, 19.1) | 597.2 (569.7, 625.9) | 175 (36) | 19.6 (18.3, 20.9) |
|  3 children | 75 (17) | 26.8 (23.2, 31.0) | 559.5 (496.9, 629.9) | 38 (25) | 18.7 (16.2, 21.5) |  | 270 (21) | 18.1 (16.9, 19.4) | 623.2 (584.4, 664.5) | 106 (22) | 19.2 (17.6, 20.9) |
|  4+ children | 22 (5) | 29.9 (22.7, 39.4) | 509.6 (406.9, 638.1) | 6 (4) | 23.4 (15.7, 34.9) |  | 157 (12) | 19.0 (17.3, 20.9) | 640.1 (586.5, 698.5) | 58 (12) | 18.0 (16.1, 20.3) |
|  ptrend |  | 0.64 | 0.98 |  | **0.03** |  |  | **0.03** | 0.3 |  | **0.04** |
|  ptrend§ |  | 0.99 | 0.64 |  | 0.09 |  |  | 0.21 | 0.16 |  | 0.36 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Hysterectomy** |  |  |  |  |  |  |  |  |  |  |  |
|  No | 411 (97) | 27.5 (25.9, 29.2) | 549.4 (523.5, 576.5) | 154 (98) | 16.6 (15.6, 17.7) |  | 972 (86) | 17.8 (17.2, 18.5) | 594.5 (574.3, 615.4) | 364 (86) | 19.4 (18.5, 20.3) |
|  Yes | 12 (3) | 20.4 (14.0, 29.7) | 649.1 (477.8, 881.8) | 3 (2) | 9.0 (4.9, 16.5) |  | 164 (14) | 16.8 (15.2, 18.6) | 572.1 (519.2, 630.5) | 60 (14) | 18.5 (16.1, 21.1) |
|  pdiff |  | 0.13 | 0.29 |  | 0.05 |  |  | 0.31 | 0.49 |  | 0.52 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Uniliateral oophorectomy** |  |  |  |  |  |  |  |  |  |  |
|  No | 477 (98) | 27.7 (26.2, 29.2) | 556.5 (531.2, 583.0) | 173 (99) | 16.6 (15.7, 17.7) |  | 1355 (96) | 18.2 (17.6, 18.7) | 616.0 (598.7, 633.9) | 519 (96) | 19.6 (18.9, 20.3) |
|  Yes | 8 (2) | 22.6 (14.6, 35.1) | 526.2 (361.2, 766.7) | 2 (1) | 11.7 (6.4, 21.7) |  | 62 (4) | 16.1 (13.9, 18.7) | 626.9 (543.9, 722.6) | 19 (4) | 21.7 (17.6, 26.7) |
| pdiff |  | 0.37 | 0.77 |  | 0.27 |  |  | 0.13 | 0.81 |  | 0.35 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Age at menopause** |  |  |  |  |  |  |  |  |  |  |  |
|  <= 47 years |  |  |  |  |  |  | 341 (31) | 16.1 (15.2, 17.2) | 640.5 (603.9, 679.3) | 124 (30) | 21.1 (19.4, 22.9) |
|  48 - 51 years |  |  |  |  |  |  | 397 (36) | 17.4 (16.5, 18.4) | 606.5 (575.2, 639.5) | 157 (38) | 19.7 (18.3, 21.2) |
|  > 51 years |  |  |  |  |  |  | 351 (32) | 19.0 (17.9, 20.2) | 657.7 (621.0, 696.6) | 130 (32) | 18.5 (17.1, 20.1) |
|  ptrend |  |  |  |  |  |  |  | **0.0005** | 0.69 |  | **0.04** |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Type of HRT** |  |  |  |  |  |  |  |  |  |  |  |
|  Never used HRT |  |  |  |  |  |  | 779 (75) | 18.6 (17.6, 19.7) | 618.4 (585.1, 653.6) | 319 (81) | 20.1 (18.8, 21.4) |
|  Estrogen alone |  |  |  |  |  |  | 81 (8) | 14.9 (12.3, 18.1) | 603.9 (501.3, 727.6) | 20 (5) | 19.2 (14.3, 25.7) |
|  Estrogen + Progestin |  |  |  |  |  |  | 177 (17) | 16.6 (14.3, 19.3) | 563.5 (488.8, 649.7) | 54 (14) | 16.0 (13.1, 19.5) |
| pdiff, E alone vs. never |  |  |  |  |  |  | **0.04** | 0.83 |  | 0.76 |
| pdiff, E+P vs. never |  |  |  |  |  |  | 0.25 | 0.31 |  | 0.06 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Ovulatory cycles¶** |  |  |  |  |  |  |  |  |  |  |
|  <= 368 | 143 (34) | 27.1 (23.1, 31.9) | 520.5 (456.0, 594.2) | 56 (39) | 18.4 (15.4, 21.8) |  | 236 (22) | 17.7 (16.1, 19.5) | 672.0 (614.3, 735.1) | 88 (21) | 19.5 (17.1, 22.3) |
|  369-414 | 120 (29) | 26.8 (23.8, 30.2) | 519.0 (471.1, 571.8) | 49 (34) | 15.2 (13.2, 17.4) |  | 263 (24) | 17.7 (16.4, 19.0) | 613.8 (573.4, 657.1) | 93 (23) | 21.8 (19.7, 24.1) |
|  415-450 | 80 (19) | 28.8 (24.5, 33.8) | 605.3 (529.5, 692.0) | 26 (18) | 18.0 (14.3, 22.6) |  | 279 (25) | 17.5 (16.3, 18.8) | 624.6 (584.1, 668.0) | 110 (27) | 17.9 (16.3, 19.7) |
|  > 450 | 73 (18) | 30.0 (24.4, 36.8) | 596.3 (503.3, 706.5) | 14 (10) | 13.5 (9.9, 18.5) |  | 318 (29) | 17.0 (15.7, 18.3) | 585.3 (544.2, 629.5) | 122 (30) | 19.4 (17.5, 21.5) |
|  ptrend |  | 0.54 | 0.26 |  | 0.20 |  |  | 0.54 | 0.05 |  | 0.87 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **BMI (kg/m2)** |  |  |  |  |  |  |  |  |  |  |  |
|  <18.5  | 9 (2) | 27.6 (18.3, 41.5) | 433.4 (306.6, 612.6) | 1 (1) | 16.5 (6.6, 41.6) |  | 21 (2) | 21.0 (16.4, 26.8) | 483.1 (382.2, 610.7) | 6 (1) | 25.5 (17.5, 37.0) |
|  18.5-24.99 | 267 (59) | 27.0 (25.1, 29.1) | 552.5 (519.1, 588.0) | 94 (62) | 16.2 (14.8, 17.7) |  | 589 (43) | 17.6 (16.8, 18.5) | 608.3 (581.6, 636.3) | 225 (44) | 20.3 (19.2, 21.6) |
|  25 - 29.99 | 131 (29) | 27.6 (24.8, 30.7) | 599.0 (547.6, 655.3) | 43 (28) | 18.1 (15.8, 20.8) |  | 522 (39) | 18.2 (17.3, 19.1) | 622.4 (594.0, 652.2) | 208 (41) | 19.2 (18.1, 20.4) |
|  >=30 | 46 (10) | 26.1 (21.9, 31.3) | 475.7 (408.2, 554.2) | 14 (9) | 16.0 (12.6, 20.4) |  | 223 (16) | 19.1 (17.6, 20.6) | 674.8 (625.6, 727.7) | 70 (14) | 19.8 (17.7, 22.1) |
|  ptrend |  | 0.84 | 0.59 |  | 0.70 |  |  | 0.24 | **0.008** |  | 0.31 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Smoking** |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 273 (57) | 27.9 (25.9, 30.0) | 543.6 (510.1, 579.3) | 97 (56) | 15.2 (13.9, 16.6) |  | 817 (59) | 18.7 (18.0, 19.4) | 606.1 (583.7, 629.4) | 319 (60) | 18.2 (17.3, 19.1) |
|  Former | 114 (24) | 28.0 (24.9, 31.5) | 582.0 (526.0, 643.8) | 39 (23) | 15.5 (13.5, 17.8) |  | 310 (22) | 18.8 (17.7, 20.1) | 659.7 (620.3, 701.6) | 108 (20) | 18.4 (16.9, 20.0) |
|  Current | 94 (20) | 26.3 (23.1, 30.0) | 565.0 (505.7, 631.4) | 37 (21) | 22.5 (19.5, 26.0) |  | 266 (19) | 15.9 (14.8, 17.0) | 595.6 (557.1, 636.8) | 102 (19) | 26.8 (24.5, 29.3) |
| pdiff, former vs. never | 0.94 | 0.28 |  | 0.80 |  |  | 0.82 | **0.02** |  | 0.83 |
| pdiff, current vs. never | 0.46 | 0.56 |  | **<0.0001** |  |  | **0.0001** | 0.66 |  | **<0.0001** |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Packyears (among current smokers)** |  |  |  |  |  |  |  |  |  |
|  <=11 | 34 (37) | 31.5 (23.9, 41.6) | 621.5 (515.0, 750.1) | 11 (31) | 23.2 (6.4, 84.8) |  | 53 (21) | 19.6 (16.6, 23.2) | 564.9 (485.1, 657.7) | 24 (25) | 24.1 (19.3, 30.0) |
|  12-19 | 21 (23) | 24.9 (17.9, 34.8) | 547.7 (437.0, 686.4) | 9 (25) | 13.3 (3.1, 57.4) |  | 67 (26) | 13.2 (11.3, 15.4) | 630.2 (547.7, 725.2) | 23 (24) | 26.3 (20.8, 33.3) |
|  20-31 | 26 (28) | 21.8 (15.8, 29.9) | 542.6 (437.7, 672.6) | 11 (31) | 34.3 (8.9, 132.2) |  | 68 (26) | 18.3 (15.9, 21.2) | 600.0 (526.0, 684.5) | 26 (27) | 28.9 (23.3, 35.8) |
|  >31 | 12 (13) | 30.8 (19.2, 49.5) | 549.7 (398.9, 757.4) | 5 (14) | 18.5 (4.3, 79.5) |  | 69 (27) | 15.5 (13.3, 18.0) | 597.1 (520.4, 685.2) | 24 (25) | 28.4 (22.9, 35.2) |
|  ptrend |  | 0.55 | 0.61 |  | 0.85 |  |  | 0.38 | 0.75 |  | 0.28 |
| \*Includes 1 control missing CA125 and 8 missing CA153; \*\* Restricted to 713 controls; †Geometric means adjusted for BMI, parity, OC use, hysterectomy, and smoking status, plus the matching factors, including study center (grouped by country), age at blood draw, fasting status, date of blood draw, menstrual cycle phase for premenopausal women at blood, OC/HRT use at blood, length of follow up. Models in postmenopausal women are additionally adjusted for oophorectomy, age at menopause, and type of HRT. P values based on continuous variables; ‡p difference between pre- and postmenopausal: CA125: <0.0001; CA15.3: 0.08; HE4: 0.78; § Trend among parous women; ¶time between menarche and menopause with time subtracted for oral contraceptive use, pregnancy and breastfeeding**;** categories based on quartile cutpoints |

|  |
| --- |
| **Table S3. Association between epidemiologic characteristics and CA125, CA15.3, and HE4 by menopausal status at blood collection in women with ovarian cancer: EPIC\*** |
|  | **PREMENOPAUSAL**  |  | **POSTMENOPAUSAL** |
|  |  | **CA125 (U/mL)** | **CA15.3 (mU/mL)** | **HE4 (pM)** |  |  | **CA125 (U/mL)** | **CA15.3 (mU/mL)** | **HE4 (pM)** |
|  | **N\* (%)** | **Mean (95% CI)†** | **Mean (95% CI)†** | **N\*\* (%)** | **Mean (95% CI)†** |   | **N\* (%)** | **Mean (95% CI)†** | **Mean (95% CI)†** | **N\* (%)** | **Mean (95% CI)†** |
| **Menopausal status‡** | 201 (25) | 34.9 (28.9, 42.1) | 569.3 (506.5, 640.0) | 46 (24) | 27.4 (19.5, 38.4) |  | 590 (75) | 25.5 (23.3, 27.9) | 644.2 (609.3, 681.2) | 147 (76) | 29.6 (25.6, 34.2) |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Age at blood draw** |  |  |  |  |  |  |  |  |  |  |  |
|  < 41 | 30 (15) | 30.8 (21.5, 44.3) | 639.7 (511.0, 800.7) | 8 (17) | 19.9 (9.8, 40.7) |  |  -- |  -- |  -- |  -- |  -- |
|  41-50 | 109 (54) | 35.9 (30.1, 42.9) | 538.1 (482.3, 600.5) | 27 (59) | 25.2 (18.6, 34.3) |  | 20 (3) | 27.6 (17.7, 43.1) | 420.7 (319.8, 553.3) | 2 (1) | 18.5 (5.8, 58.8) |
|  51-60 | 62 (31) | 35.5 (27.2, 46.3) | 585.8 (496.6, 691.0) | 11 (24) | 20.7 (11.0, 39.1) |  | 296 (50) | 26.2 (23.3, 29.4) | 678.6 (631.6, 729.1) | 70 (48) | 28.1 (23.0, 34.4) |
|  61-70 |  -- |  -- |  -- |  -- |  -- |  | 241 (41) | 24.2 (21.3, 27.5) | 642.8 (594.2, 695.5) | 61 (41) | 34.9 (28.2, 43.1) |
|  > 70 |  -- |  -- |  -- |  -- |  -- |  | 33 (6) | 27.6 (19.1, 39.9) | 547.1 (435.8, 686.8) | 14 (10) | 35.0 (21.4, 57.1) |
|  ptrend |  | 0.61 | 0.67 |  | 0.93 |  |  | 0.60 | 0.90 |  | 0.16 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Age at menarche** |  |  |  |  |  |  |  |  |  |  |
|  < 12 | 34 (18) | 34.5 (24.9, 47.6) | 536.2 (439.7, 654.0) | 11 (25) | 25.6 (15.4, 42.5) |  | 70 (12) | 25.2 (19.9, 31.8) | 653.0 (564.1, 755.9) | 17 (12) | 32.4 (22.0, 47.8) |
|  12 | 45 (24) | 34.4 (26.2, 45.1) | 540.3 (457.4, 638.1) | 7 (16) | 17.3 (10.7, 28.0) |  | 85 (15) | 23.1 (18.7, 28.5) | 567.1 (497.0, 647.2) | 19 (14) | 28.2 (19.6, 40.5) |
|  13 | 60 (31) | 34.6 (27.5, 43.6) | 573.4 (497.5, 660.8) | 15 (34) | 15.6 (10.6, 22.9) |  | 127 (22) | 24.6 (20.8, 29.2) | 663.9 (596.6, 738.8) | 27 (20) | 26.4 (19.5, 35.9) |
|  14 | 28 (15) | 29.9 (20.9, 42.6) | 646.3 (519.8, 803.5) | 6 (14) | 19.3 (9.8, 38.0) |  | 143 (25) | 26.7 (22.7, 31.5) | 661.4 (596.8, 732.9) | 38 (28) | 30.8 (23.8, 39.7) |
|  > 14 | 24 (13) | 40.7 (27.8, 59.8) | 510.9 (403.8, 646.4) | 5 (11) | 83.2 (36.9, 187.6) |  | 141 (25) | 25.2 (21.4, 29.6) | 644.0 (581.4, 713.3) | 37 (27) | 32.5 (24.9, 42.4) |
|  ptrend |  | 0.80 | 0.69 |  | 0.48 |  |  | 0.61 | 0.50 |  | 0.73 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Oral contraceptive use** |  |  |  |  |  |  |  |  |  |
|  Never | 80 (42) | 36.0 (29.0, 44.8) | 551.9 (482.7, 631.1) | 20 (45) | 21.7 (13.9, 33.7) |  | 349 (61) | 25.6 (23.0, 28.5) | 648.4 (606.2, 693.4) | 87 (62) | 31.6 (26.5, 37.8) |
|  Ever | 111 (58) | 33.4 (27.9, 40.0) | 566.6 (507.4, 632.7) | 24 (55) | 22.9 (15.6, 33.7) |  | 224 (39) | 24.9 (21.7, 28.6) | 625.0 (573.6, 681.1) | 53 (38) | 30.3 (23.9, 38.5) |
| pdiff |  | 0.63 | 0.79 |  | 0.88 |  |  | 0.79 | 0.53 |  | 0.80 |
|  >= 2 years | 42 (22) | 40.7 (30.8, 53.8) | 546.6 (460.8, 648.4) | 9 (21) | 28.7 (15.0, 55.0) |  | 65 (12) | 21.5 (16.8, 27.4) | 621.2 (534.1, 722.5) | 13 (10) | 23.0 (14.5, 36.3) |
|  > 2 -5 years | 24 (13) | 24.4 (16.8, 35.4) | 555.8 (442.6, 698.0) | 5 (12) | 19.3 (6.4, 58.3) |  | 49 (9) | 28.0 (21.2, 37.1) | 704.9 (593.2, 837.6) | 12 (9) | 36.1 (22.6, 57.7) |
|  > 5 -10 years | 24 (13) | 37.6 (25.1, 56.4) | 536.4 (418.8, 686.9) | 4 (9) | 19.6 (6.2, 62.2) |  | 55 (10) | 25.9 (19.9, 33.7) | 633.0 (537.6, 745.3) | 12 (9) | 31.2 (19.4, 50.1) |
|  > 10 years | 17 (9) | 27.4 (16.9, 44.4) | 677.4 (504.5, 909.4) | 5 (12) | 19.1 (6.5, 56.3) |  | 40 (7) | 21.3 (15.4, 29.5) | 448.3 (367.2, 547.2) | 9 (7) | 29.6 (16.7, 52.2) |
|  ptrend |  | 0.24 | 0.26 |  | 0.69 |  |  | 0.47 | **0.001** |  | 0.87 |
|  ptrend§ |  | 0.41 | 0.27 |  | 0.05 |  |  | 0.95 | **0.0008** |  | 0.58 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Parity** |  |  |  |  |  |  |  |  |  |  |  |
|  Nulliparous | 40 (21) | 31.5 (23.7, 42.0) | 611.8 (513.0, 729.6) | 14 (32) | 12.7 (8.6, 18.6) |  | 87 (16) | 29.4 (23.9, 36.2) | 595.3 (523.2, 677.4) | 25 (18) | 33.1 (24.4, 45.1) |
|  Parous | 150 (79) | 35.3 (30.6, 40.7) | 549.1 (502.9, 599.6) | 30 (68) | 29.1 (23.1, 36.7) |  | 460 (84) | 24.6 (22.5, 26.9) | 645.3 (610.3, 682.3) | 112 (82) | 30.0 (26.1, 34.5) |
| pdiff |  | 0.49 | 0.29 |  | **0.005** |  |  | 0.12 | 0.26 |  | 0.57 |
|  1 child | 35 (19) | 32.4 (23.7, 44.4) | 650.3 (539.3, 784.0) | 6 (15) | 29.0 (12.6, 67.2) |  | 77 (14) | 23.9 (19.1, 29.9) | 629.9 (547.3, 725.0) | 25 (19) | 28.5 (20.7, 39.2) |
|  2 children | 76 (41) | 35.9 (29.0, 44.4) | 516.8 (455.3, 586.7) | 11 (27) | 25.9 (16.7, 40.1) |  | 216 (40) | 25.4 (22.2, 28.9) | 628.6 (578.4, 683.1) | 47 (35) | 32.8 (26.2, 41.2) |
|  3 children | 20 (11) | 35.1 (22.9, 53.7) | 466.4 (362.0, 601.0) | 6 (15) | 28.2 (12.3, 64.7) |  | 99 (18) | 23.3 (19.1, 28.3) | 687.9 (608.4, 777.8) | 24 (18) | 31.2 (22.6, 43.0) |
|  4+ children | 13 (7) | 42.1 (24.7, 71.8) | 552.2 (402.1, 758.4) | 4 (10) | 42.1 (18.9, 93.6) |  | 59 (11) | 25.8 (19.9, 33.5) | 664.2 (564.3, 781.9) | 13 (10) | 27.9 (17.5, 44.4) |
|  ptrend |  | 0.39 | **0.04** |  | **0.006** |  |  | 0.30 | 0.14 |  | 0.79 |
|  ptrend§ |  | 0.34 | 0.18 |  | 0.86 |  |  | 0.86 | 0.33 |  | 0.78 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Hysterectomy** |  |  |  |  |  |  |  |  |  |  |  |
|  No | 172 (98) | 34.3 (30.0, 39.1) | 555.9 (513.1, 602.3) | 41 (98) | 22.9 (18.4, 28.5) |  | 412 (86) | 24.4 (22.2, 26.8) | 630.9 (595.1, 668.9) | 107 (91) | 28.5 (24.7, 32.9) |
|  Yes | 4 (2) | 23.2 (8.5, 63.6) | 611.5 (332.6, 1124.4) | 1 (2) | 15.0 (2.5, 88.9) |  | 65 (14) | 30.3 (23.0, 39.8) | 665.2 (563.5, 785.2) | 10 (9) | 42.9 (23.1, 79.7) |
| pdiff |  | 0.46 | 0.76 |  | 0.65 |  |  | 0.16 | 0.57 |  | 0.23 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Uniliateral oophorectomy** |  |  |  |  |  |  |  |  |  |  |
|  No | 197 (98) | 35.2 (31.2, 39.8) | 571.6 (529.7, 616.7) | 46 (100) |  -- |  | 575 (97) | 25.5 (23.5, 27.6) | 646.5 (615.0, 679.6) | 144 (98) | 30.9 (27.3, 35.0) |
|  Yes | 4 (2) | 24.6 (9.6, 63.0) | 376.4 (210.0, 674.6) | 0 (0) |  -- |  | 15 (3) | 23.9 (14.5, 39.6) | 596.5 (435.9, 816.3) | 3 (2) | 52.0 (20.4, 132.5) |
| pdiff |  | 0.46 | 0.17 |  |  |  |  | 0.81 | 0.62 |  | 0.28 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Age at menopause** |  |  |  |  |  |  |  |  |  |  |  |
|  ≤ 47 years |  |  |  |  |  |  | 111 (25) | 26.0 (21.5, 31.3) | 655.9 (583.0, 737.8) | 21 (18) | 30.7 (22.2, 42.5) |
|  48 - 51 years |  |  |  |  |  |  | 175 (39) | 23.2 (20.0, 27.0) | 683.9 (623.1, 750.7) | 37 (32) | 39.6 (30.6, 51.1) |
|  > 51 years |  |  |  |  |  |  | 166 (37) | 24.8 (21.3, 28.9) | 609.2 (553.6, 670.4) | 57 (50) | 26.8 (21.9, 32.8) |
|  ptrend |  |  |  |  |  |  |  | 0.69 | 0.37 |  | 0.41 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Type of HRT** |  |  |  |  |  |  |  |  |  |  |  |
|  Never used HRT |  |  |  |  |  |  | 330 (75) | 27.1 (23.1, 31.8) | 646.9 (583.8, 716.9) | 85 (79) | 33.6 (26.0, 43.5) |
|  Estrogen alone |  |  |  |  |  |  | 36 (8) | 16.5 (9.7, 28.0) | 683.9 (487.7, 959.0) | 5 (5) | 16.0 (4.5, 57.0) |
|  Estrogen + Progestin |  |  |  |  |  |  | 74 (17) | 24.5 (16.0, 37.4) | 579.5 (442.5, 759.0) | 18 (17) | 29.2 (12.8, 66.3) |
| pdiff, E alone vs. never |  |  |  |  |  |  |  | 0.13 | 0.79 |  | 0.30 |
| pdiff, E+P vs. never |  |  |  |  |  |  |  | 0.71 | 0.53 |  | 0.78 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Ovulatory cycles¶** |  |  |  |  |  |  |  |  |  |  |  |
|  <= 368 | 57 (32) | 39.7 (27.0, 58.5) | 463.2 (369.3, 580.9) | 12 (31) | 54.9 (31.2, 96.6) |  | 76 (16) | 26.2 (20.9, 32.9) | 656.6 (568.4, 758.5) | 19 (16) | 33.6 (23.0, 49.3) |
|  369-414 | 44 (25) | 37.8 (28.3, 50.5) | 490.1 (413.6, 580.8) | 13 (33) | 25.2 (16.1, 39.5) |  | 125 (27) | 21.7 (18.2, 25.9) | 673.7 (602.8, 753.0) | 25 (21) | 32.4 (23.3, 45.2) |
|  415-450 | 50 (28) | 31.5 (22.9, 43.2) | 638.7 (530.2, 769.4) | 9 (23) | 14.6 (8.2, 25.7) |  | 121 (26) | 28.7 (24.0, 34.4) | 660.9 (590.2, 739.9) | 28 (24) | 30.0 (22.2, 40.6) |
|  > 450 | 28 (16) | 29.4 (18.2, 47.7) | 732.8 (552.3, 972.2) | 5 (13) | 5.5 (2.5, 12.3) |  | 140 (30) | 23.9 (20.2, 28.2) | 587.3 (528.9, 652.1) | 45 (38) | 29.7 (23.4, 37.8) |
|  ptrend |  | 0.43 | **0.04** |  | **0.003** |  |  | 0.99 | 0.15 |  | 0.56 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **BMI (kg/m2)** |  |  |  |  |  |  |  |  |  |  |  |
|  <18.5  | 1 (1) | 20.4 (3.1, 135.6) | 543.7 (163.8, 1804.9) | 0 (0) |  |  | 4 (1) | 10.9 (4.1, 29.4) | 630.9 (338.0, 1177.5) | 2 (1) | 57.9 (17.8, 188.4) |
|  18.5-24.99 | 111 (58) | 33.5 (28.3, 39.7) | 564.5 (506.9, 628.6) | 23 (58) | 22.4 (15.8, 31.8) |  | 252 (45) | 25.0 (22.1, 28.3) | 637.4 (588.9, 689.8) | 61 (44) | 30.0 (24.5, 36.8) |
|  25 - 29.99 | 54 (28) | 30.9 (24.2, 39.5) | 554.7 (475.0, 647.8) | 11 (28) | 15.6 (9.9, 24.6) |  | 193 (34) | 25.5 (22.1, 29.3) | 651.8 (596.3, 712.4) | 48 (34) | 32.4 (25.7, 40.8) |
|  >=30 | 27 (14) | 50.1 (35.0, 71.7) | 637.5 (507.9, 800.1) | 6 (15) | 61.8 (26.1, 146.2) |  | 114 (20) | 25.9 (21.5, 31.2) | 680.4 (604.8, 765.5) | 29 (21) | 28.9 (21.1, 39.7) |
|  ptrend |  | 0.11 | 0.44 |  | 0.26 |  |  | 0.58 | 0.38 |  | 0.74 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Smoking** |  |  |  |  |  |  |  |  |  |  |  |
|  Never | 101 (51) | 38.5 (32.4, 45.9) | 541.5 (485.3, 604.3) | 25 (56) | 24.7 (17.8, 34.4) |  | 323 (56) | 26.5 (23.8, 29.6) | 642.2 (599.6, 687.9) | 92 (64) | 32.3 (27.4, 38.0) |
|  Former | 52 (26) | 35.1 (27.4, 45.0) | 590.2 (504.9, 689.9) | 8 (18) | 17.9 (9.2, 34.7) |  | 128 (22) | 26.3 (22.1, 31.3) | 613.7 (549.6, 685.2) | 26 (18) | 26.4 (19.2, 36.4) |
|  Current | 47 (24) | 28.4 (21.8, 37.1) | 595.8 (504.0, 704.2) | 12 (27) | 24.8 (14.4, 42.7) |  | 126 (22) | 22.6 (19.0, 27.0) | 680.4 (608.5, 760.8) | 25 (17) | 33.8 (24.3, 47.1) |
| pdiff, former vs. never |  | 0.56 | 0.38 |  | 0.43 |  |  | 0.92 | 0.50 |  | 0.29 |
| pdiff, current vs. never |  | 0.07 | 0.36 |  | 0.99 |  |  | 0.14 | 0.40 |  | 0.81 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Packyears (among current smokers)** |  |  |  |  |  |  |  |  |  |
|  <=11 packyears | 15 (32) | 30.5 (15.8, 58.9) | 536.6 (373.5, 770.8) | 4 (33) | 23.0 (11.1, 47.6) |  | 26 (21) | 19.0 (13.4, 26.8) | 611.0 (486.5, 767.5) | 6 (24) | 27.3 (9.2, 81.0) |
|  12-19 | 15 (32) | 54.1 (29.4, 99.5) | 561.6 (401.3, 785.9) | 4 (33) | 23.9 (10.7, 53.3) |  | 27 (22) | 34.2 (24.1, 48.6) | 724.6 (575.0, 913.1) | 3 (12) | 39.4 (7.2, 216.1) |
|  20-31 | 12 (26) | 17.6 (9.1, 34.2) | 745.9 (517.2, 1075.5) | 4 (33) | 42.5 (18.7, 97.0) |  | 31 (25) | 18.4 (13.4, 25.2) | 703.3 (569.0, 869.4) | 6 (24) | 28.4 (10.7, 75.2) |
|  >31 | 5 (11) | 16.7 (5.5, 50.6) | 850.2 (461.6, 1566.0) | 0 (0) |  |  | 38 (31) | 19.8 (14.8, 26.6) | 721.8 (594.3, 876.7) | 10 (40) | 48.0 (22.5, 102.6) |
|  ptrend |   | 0.24 | 0.62 |   | 0.46 |   |   | 0.72 | 0.40 |   | 0.21 |
| \*Includes 1 control missing CA125 and 8 missing CA153; \*\* Restricted to 193 cases; †geometric means adjusted for matching factors, including study center (grouped by country), age at blood draw, fasting status, date and time of blood draw, menopausal status at blood, menstrual cycle phase for premenopausal women at blood, OC/HRT use at blood, length of follow up. HRT use and hysterectomy are each additionally adjusted for the other. P values based on continuous variables; ‡p difference between pre- and postmenopausal: CA125 = 0.01; CA15.3 = 0.10; HE4 = 0.72; § Trend among parous women; ¶time between menarche and menopause with time subtracted for oral contraceptive use, pregnancy and breastfeeding; categories based on quartile cutpoints |