**Additional material**

**Exposure to airborne cadmium and breast cancer stage, grade and histology at diagnosis: Findings from the E3N cohort study**

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**Additional** **Table 1**: Demographic and lifestyle characteristics of cases according to grade of differentiation of breast cancer at diagnosis in the case-control study nested within the E3N cohort, France, 1990-2008

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristics | Grade 1n (%)=548 (16.0%) | Grade 2n (%)=1,263 (36.8%) | Grade 3n (%)=1,621 (47.2%) | *P* value |
| Cumulative airborne cadmium exposure (mg/m2), mean ± SD | 19.0 ± 120.8 | 13.0 ± 61.6 | 10.4 ± 31.9 | 0.885 |
| Age at recruitment (years), mean ± SD | 49.5 ± 5.9 | 49.8 ± 6.3  | 49.8 ± 6.4 | 0.770 |
| Age at diagnosis (years), mean ± SD | 59.1 ± 7.3 | 59.0 ± 7.6  | 60.0 ± 7.7 | <0.001 |
| Alcohol drinking (g/day), n (%) |  |  |  |  |
|  Never | 57 (10.4) | 110 (8.7) | 144 (8.9) |  |
|  < 6.7 | 150 (27.4) | 364 (28.8) | 468 (28.9) |  |
|  ≥ 6.7 | 254 (46.3) | 529 (41.9) | 731 (45.1) |  |
|  Missing  | 87 (15.9) | 260 (20.6) | 278 (17.1) | 0.101 |
| Body Mass Index (kg/m²), n (%) |  |  |  |  |
|  < 25 | 475 (86.7) | 1,046 (82.8) | 1,323 (81.6) |  |
|  25 - <30 | 63 (11.5) | 177 (14.0) | 252 (15.6) |  |
|  ≥ 30 | 10 (1.8) | 40 (3.2) | 46 (2.8) | 0.073 |
| Smoking status, n (%) |  |  |  |  |
|  Never  | 298 (54.4) | 697 (55.2) | 871 (53.7) |  |
|  Current  | 79 (14.4) | 180 (14.2) | 247 (15.2) |  |
|  Former  | 171 (31.2) | 386 (30.6) | 503 (31.0) | 0.930 |
| Status of birthplace, n (%) |  |  |  |  |
|  Rural | 128 (23.4) | 359 (28.4) | 438 (27.0) |  |
|  Urban | 382 (69.7) | 804 (63.5) | 1,023 (63.1) |  |
|  Missing  | 38 (6.9) | 102 (8.1) | 160 (9.9) | 0.020 |
| Physical activity (METs-h/week), n (%) |  |  |  |
|  < 25.3 | 128 (23.4) | 338 (26.8) | 379 (23.4) |  |
|  25.3 - 37.3 | 182 (33.2) | 372 (29.4) | 514 (31.7) |  |
|  37.4 - 56.9 | 140 (25.5) | 340 (26.9) | 423 (26.1) |  |
|  ≥ 57.0 | 98 (17.9) | 213 (16.9) | 305 (18.8) | 0.266 |
| Education, n (%) |  |  |  |  |
|  Secondary | 73 (13.3) | 155 (12.3) | 194 (12.0) |  |
|  1- to 2-year university degree | 260 (47.5) | 646 (51.1) | 834 (51.4) |  |
|  ≥ 3 year university degree | 215 (39.2) | 462 (36.6) | 593 (36.6) | 0.581 |
| Menopausal status, n (%) |  |  |  |  |
|  Premenopausal  | 98 (17.9) | 272 (21.5) | 254 (15.7) |  |
|  Postmenopausal | 450 (82.1) | 991 (78.5) | 1,367 (84.3) | <0.001 |
| Use of oral contraceptives, n (%) |  |  |  |
|  No  | 220 (40.1) | 533 (42.2) | 645 (39.8) |  |
|  Yes | 328 (59.9) | 730 (57.8) | 976 (60.2) | 0.406 |
| Use of MHT, n (%) |  |  |  |  |
|  No  | 446 (81.4) | 1,056 (83.6) | 1,318 (81.3) |  |
|  Yes | 102 (18.6) | 207 (16.4) | 303 (18.7) | 0.242 |
| Parity & Age at First Pregnancy (AFP), n (%) |  |  |  |
|  0 | 74 (13.5) | 171 (13.5) | 202 (12.5) |  |
|  1-2 & AFP < 30 | 282 (51.5) | 611 (48.4) | 822 (50.7) |  |
|  1-2 & AFP ≥ 30 | 53 (9.7) | 147 (11.6) | 182 (11.2) |  |
|  ≥ 3 | 139 (25.3) | 334 (26.4) | 415 (25.6) | 0.754 |
| Age at menarche, n (%) |  |  |  |  |
|  < 12 | 118 (21.5) | 265 (21.0) | 354 (21.8) |  |
|  12 - 13 | 279 (50.9) | 675 (53.4) | 850 (52.4) |  |
|  ≥ 14 | 151 (27.6) | 323 (25.6) | 417 (25.7) | 0.851 |
| Breastfeeding, n (%) |  |  |  |  |
|  No  | 261 (47.6) | 605 (47.9) | 760 (46.9) |  |
|  Yes | 287 (52.4) | 658 (52.1) | 861 (53.1) | 0.856 |
| Family history of breast cancer, n (%) |  |  |  |
|  No  | 463 (84.5) | 1,008 (79.8) | 1,335 (82.4) |  |
|  Yes | 85 (15.5) | 255 (20.2) | 286 (17.6) | 0.042 |
| History of personal benign breast disease, n (%) |  |  |
|  No  | 368 (67.2) | 897 (71.0) | 1,143 (70.5) |  |
|  Yes | 180 (32.8) | 366 (29.0) | 478 (29.5) | 0.233 |
| Mammography before inclusion, n (%) |  |  |  |
|  No  | 113 (20.6) | 264 (20.9) | 384 (23.7) |  |
|  Yes | 435 (79.4) | 999 (79.1) | 1,237 (76.3) | 0.128 |
| ER status, n (%) |  |  |  |  |
|  ER -  | 43 (7.8) | 145 (11.5) | 352 (21.7) |  |
|  ER + | 401 (73.2) | 898 (71.1) | 1,053 (65.0) |  |
|  Missing | 104 (19.0) | 220 (17.4) | 216 (13.3) | <0.001 |
| PR status, n (%) |  |  |  |  |
|  PR -  | 121 (22.1) | 279 (22.1) | 580 (35.8) |  |
|  PR + | 298 (54.4) | 731 (57.9) | 780 (48.1) |  |
|  Missing | 129 (23.5) | 253 (20.0) | 261 (16.1) | <0.001 |

The analyses were done on the three main type of grade after excluding grade 4 (1 case) and those with missing grade information (971 cases)

P values estimated based on Kruskal Wallis test for continuous variables and Chi-square test for categorical variables
SD: Standard deviation, MET: Metabolic Equivalent of Task, MHT: menopausal hormone replacement therapy, Menopausal status at index date: date of diagnosis of the case in the case-control pair, ER: estrogen receptor, PR: estrogen receptor

**Additional** **Table 2**: Demographic and lifestyle characteristics of cases according to histological type of breast cancer at diagnosis in the case-control study nested within the E3N cohort, France, 1990-2008

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristics | IDCn (%)=2,940 (16.0%) | ILCn (%)=676 (36.9%) | ITC n (%)=132 (36.9%) | ID and ILCn (%)=109 (47.1%) | *P* value |
| Cumulative airborne cadmium exposure (mg/m2), mean ± SD | 13.1 ± 68.9 | 10.3 ± 27.7 | 19.2 ± 70.9 | 16.5 ± 66.9 | 0.227 |
| Age at recruitment (years), mean ± SD | 49.6 ± 6.3 | 50.3 ± 6.4 | 49.2 ± 5.4 | 49.3 ± 6.0 | 0.078 |
| Age at diagnosis (years), mean ± SD | 59.1 ± 7.7  | 59.8 ± 7.8 | 58.9 ± 6.7 | 58.4 ± 7.5 | 0.126 |
| Alcohol drinking (g/day), n (%) |  |  |  |
|  Never | 271 (9.2) | 59 (8.7) | 14 (10.7) | 4 (3.6) |  |
|  < 6.7 | 864 (29.4) | 189 (27.7) | 34 (25.9) | 24 (21.8) |  |
|  ≥ 6.7 | 1,270 (43.2) | 313 (45.9) | 64 (48.9) | 54 (49.1) |  |
|  Missing  | 535 (18.2) | 121 (17.7) | 19 (14.5) | 28 (25.5) | 0.137 |
| Body Mass Index (kg/m²), n (%) |  |  |
|  < 25 | 2,446 (83.2) | 568 (83.3) | 115 (87.8) | 88 (80.0) |  |
|  25 - <30 | 416 (14.2) | 91 (13.3) | 14 (10.7) | 19 (18.2) |  |
|  ≥ 30 | 78 (2.6) | 23 (3.4) | 2 (1.5) | 2 (1.8) | 0.512 |
| Smoking status, n (%) |  |  |  |  |  |
|  Never  | 1,601 (54.5) | 355 (52.1) | 70 (53.4) | 52 (47.3) |  |
|  Current  | 413 (14.0) | 114 (16.7) | 25 (18.1) | 19 (17.3) |  |
|  Former  | 926 (31.5) | 213 (31.2) | 36 (27.5) | 39 (35.4) | 0.267 |
| Status of birthplace, n (%) |  |  |  |  |  |
|  Rural | 778 (26.5) | 182 (26.7) | 28 (21.4) | 27 (24.6) |  |
|  Urban | 1,898 (64.5) | 434 (63.6) | 93 (71.0) | 72 (65.4) |  |
|  Missing  | 264 (9.0) | 66 (9.7) | 10 (7.6) | 11 (10.0) | 0.803 |
| Physical activity (METs-h/week), n (%) |  |  |  |  |
|  < 25.3 | 726 (24.7) | 163 (23.9) | 32 (24.4) | 24 (21.8) |  |
|  25.3 - 37.3 | 933 (31.7) | 205 (30.1) | 40 (30.5) | 45 (40.9) |  |
|  37.4 - 56.9 | 764 (26.0) | 198 (29.0) | 38 (29.0) | 23 (20.9) |  |
|  ≥ 57.0 | 517 (17.6) | 116 (17.0) | 21 (16.0) | 18 (16.4) | 0.541 |
| Education, n (%) |  |  |  |  |  |
|  Secondary | 363 (12.3) | 70 (10.3) | 17 (13.0) | 14 (12.7) |  |
|  1 to 2 year university degree | 1,504 (51.2) | 344 (50.4) | 59 (45.0) | 55 (50.0) |  |
|  ≥ 3 year university degree | 1,073 (36.5) | 268 (39.3) | 55 (42.0) | 41 (37.3) | 0.528 |
| Menopausal status, n (%) |  |  |  |  |  |
|  Premenopausal  | 598 (20.3) | 122 (17.9) | 21 (16.0) | 23 (20.9) |  |
|  Postmenopausal | 2,342 (79.7) | 560 (82.1) | 110 (84.0) | 87 (79.1) | 0.338 |
| Use of oral contraceptives, n (%) |  |  |  |  |
|  No  | 1,203 (40.9) | 270 (39.6) | 49 (37.4) | 45 (40.9) |  |
|  Yes | 1,737 (59.1) | 412 (60.4) | 82 (62.6) | 65 (59.1) | 0.809 |
| Use of MHT, n (%) |  |  |  |  |  |
|  No  | 2,439 (83.0) | 557 (81.7) | 107 (81.7) | 87 (79.1) |  |
|  Yes | 501 (17.0) | 125 (18.3) | 24 (18.3) | 23 (20.9) | 0.639 |
| Parity & Age at First Pregnancy (AFP), n (%) |  |  |  |  |
|  0 | 402 (13.7) | 78 (11.4) | 16 (12.2) | 17 (15.5) |  |
|  1-2 & AFP < 30 | 1,463 (49.8) | 324 (47.5) | 69 (52.7) | 53 (48.2) |  |
|  1-2 & AFP ≥ 30 | 322 (10.9) | 99 (14.5) | 11 (8.4) | 14 (12.7) |  |
|  ≥ 3 | 753 (25.6) | 181 (26.5) | 35 (26.7) | 26 (23.6) | 0.258 |
| Age at menarche, n (%) |  |  |  |  |  |
|  < 12 | 624 (21.2) | 138 (20.2) | 35 (26.7) | 31 (28.2) |  |
|  12-13 | 1,552 (52.8) | 366 (53.7) | 66 (50.4) | 49 (44.5) |  |
|  ≥ 14 | 764 (26.0) | 178 (26.1) | 30 (22.9) | 30 (27.3) | 0.344 |
| Breastfeeding, n (%) |  |  |  |  |  |
|  No  | 1,409 (47.9) | 302 (44.3) | 65 (49.6) | 57 (51.8) |  |
|  Yes | 1,531 (52.1) | 380 (55.7) | 66 (50.4) | 53 (48.2) | 0.251 |
| Family history of breast cancer, n (%) |  |  |  |  |
|  No  | 2,411 (82.0) | 557 (81.7) | 111 (84.7) | 82 (74.6) |  |
|  Yes | 529 (18.0) | 125 (18.3) | 20 (15.3) | 28 (25.4) | 0.192 |
| History of personal benign breast disease, n (%) |  |  |  |  |  |
|  No  | 2,063 (70.2) | 482 (70.7) | 83 (63.4) | 76 (69.1) |  |
|  Yes | 877 (29.8) | 200 (29.3) | 48 (36.6) | 34 (30.9) | 0.394 |
| Mammography before inclusion, n (%) |  |  |  |  |
|  No  | 660 (22.4) | 148 (21.7) | 24 (18.3) | 24 (21.8) |  |
|  Yes | 2,280 (77.6) | 534 (78.3) | 107 (81.7) | 86 (78.2) | 0.717 |
| ER status, n (%) |  |  |  |  |  |
|  ER -  | 522 (17.8) | 69 (10.1) | 10 (7.6) | 9 (9.2) |  |
|  ER + | 1,921 (65.3) | 481 (70.5) | 94 (71.8) | 81 (73.6) |  |
|  Missing | 497 (16.9) | 132 (19.4) | 27 (20.6) | 20 (18.2) | < 0.001 |
| PR status, n (%) |  |  |  |  |  |
|  PR -  | 875 (29.8) | 162 (23.7) | 36 (27.5) | 20 (18.2) |  |
|  PR + | 1,488 (50.6) | 375 (55.0) | 62 (47.3) | 68 (61.8) |  |
|  Missing | 577 (19.6) | 145 (21.3) | 33 (25.2) | 22 (20.0) | 0.005 |

The analyses were done on the four main type of histology after excluding other histology cases (256 cases) and those with missing histology information (288 cases)

P values estimated based on Kruskal Wallis test for continuous variables and Chi-square test for categorical variables
SD: Standard deviation, MET: Metabolic Equivalent of Task, MHT: menopausal hormone therapy, Menopausal status at index date: date of diagnosis of the case in the case-control pair, ER: estrogen receptor, PR: progesterone receptor

**Additional** **Table 3:** Odds ratio and 95% confidence intervals (OR, 95% CI) for the association of quintiles of the mean airborne cadmium exposure with risk of breast cancer according to the stage in the case-control study nested within the E3N cohort, France, 1990-2008.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Cumulative airborne cadmium exposure (mg/m2) | n cases/ controls | OR (95% CI) a | *P* trend | *P* likelihood  | *P* heterogeneity |
| Stage I |  |  |  |  |  |
|  ≤ 0.011 | 468/484 | Ref |  |  |  |
|  > 0.011 - 0.105 | 502/453 | 1.17 (0.97-1.42) |  |  |  |
|  > 0.105 - 0.375 | 477/487 | 1.03 (0.85-1.24) |  |  |  |
|  > 0.375 - 1.32 | 448/478 | 1.00 (0.83-1.22) |  |  |  |
|  > 1.32 | 475/468 | 1.04 (0.85-1.28) | 0.743 | 0.473 |  |
| Stage II |  |  |  |  |  |
|  ≤ 0.011 | 244/240 | Ref |  |  |  |
|  > 0.011 - 0.105 | 225/266 | 0.84 (0.65-1.10) |  |  |  |
|  > 0.105 - 0.375 | 264/240 | 1.18 (0.90-1.55) |  |  |  |
|  > 0.375 - 1.32 | 236/244 | 1.03 (0.77-1.36) |  |  |  |
|  > 1.32 | 247/226 | 1.11 (0.83-1.49) | 0.234 | 0.157 |  |
| Stages III-IV |  |  |  |  |  |
|  ≤ 0.011 | 76/65 | Ref |  |  |  |
|  > 0.011 - 0.105 | 70/77 | 0.79 (0.47-1.30) |  |  |  |
|  > 0.105 - 0.375 | 73/69 | 0.88 (0.53-1.45) |  |  |  |
|  > 0.375 - 1.32 | 54/59 | 0.68 (0.38-1.22) |  |  |  |
|  > 1.32 | 65/68 | 0.72 (0.40-1.30) | 0.247 | 0.698 | 0.333 |

a Multivariable models were adjusted for physical activity, smoking status, level of education, body mass index (BMI), age at menarche, age at first full-term pregnancy (AFP), parity, breastfeeding, oral contraceptive use, menopausal hormone replacement therapy use (HRT), status of birthplace, previous family history of breast cancer (FHBC), and personal history of benign breast disease

P likelihood: P-values from likelihood ratio test comparing the statistically significance of the global effect of the quintiles

P heterogeneity: comparing heterogeneity of associations across breast cancer stage at diagnosis



**Additional Figure 1: Cubic spline modelling of the relationship between cumulative airborne cadmium exposure and risk of invasive tubular breast cancer** i**n the case-control study nested within the E3N cohort, France, 1990-2008.** Multivariable adjusted OR (continuous line) and 95% CI (dotted line) obtained using four-knot restricted cubic splines with the minimum value used as reference. Models were adjusted for physical activity, smoking status, alcohol intake, level of education, body mass index, previous family history of breast cancer, personal history of benign breast disease, age at menarche, age at first full-term pregnancy, parity, breastfeeding, oral contraceptive use, menopausal hormone therapy use and status of birthplace.