Supplementary Table S1. Baseline characteristics by tertiles of CML=AGE intake (KU/1000 kcal)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Tertile 1  (n=9155) | Tertile 2  (n=9156) | Tertile 3  (n=9153) |
| CML-AGE (KU/1000 kcal) | <4806 | 4806-6639 | >6639 |
| Alcohol intake (g/day) | 5.7 (14.6) | 5.5 (11.9) | 5.4 (11.3) |
| Total energy intake (kcal/day) | 1698.3 (573.2) | 1727.0 (577.9) | 1801.4 (645.4) |
| Total fat from diet (g/day) | 44.0 (17.1) | 53.9 (20.5) | 65.8 (26.8) |
| Red meat (g/day) | 30.5 (20.7) | 50.8 (29.8) | 77.6 (50.5) |
| Red meat, very well done (g/day) | 0.4 (2.2) | 0.6 (3.4) | 1.1 (6.6) |
| Processed meat (g/day) | 5.7 (7.0) | 10.0 (10.2) | 16.4 (16.8) |
| Animal protein (g/day) | 16.6 (8.2) | 23.3 (9.8) | 31.3 (15.3) |
| Carbohydrate (g/day) | 265.7 (93.6) | 243.9 (83.9) | 228.0 (85.2) |
| Fructose (g/day) | 30.8 (18.8) | 24.7 (13.4) | 21.5 (12.4) |
| Calcium (mg/day) | 960.3 (488) | 871.6 (422.4) | 810.2 (390.1) |
| Fruit (cups/day) | 2.9 (1.8) | 2.2 (1.3) | 1.8 (1.1) |
| Vegetables (cups/day) | 2.6 (1.3) | 2.5 (1.1) | 2.3 (1.0) |
| Age (years) | 63.4 (5.4) | 62.5 (5.3) | 61.5 (5.1) |
| Breast cancer, n (%)  No  Yes | 8661 (94.6)  494 (5.4) | 8604 (94.0)  552 (6.0) | 8607 (94.0)  546 (6.0) |
| BMI (kg/m2), n (%)  < 18.5  18.5- < 25  25- < 30  >= 30 | 126 (1.4)  4525 (49.4)  3017 (33.0)  1487 (16.2) | 88 (1.0)  3513 (38.4)  3337 (36.5)  2218 (24.2) | 73 (0.8)  2819 (30.8)  3277 (35.8)  2984 (32.6) |
| Vigorous activity, n (%)  None  <1 hour/week  1 hour/week 2 hours/week  3 hours/week  4+ hours/week | 951 (10.4)  1382 (15.1)  969 (10.6)  1632 (17.8)  1744 (19.1)  2477 (27.1) | 1255 (13.7)  1692 (18.5)  1143 (12.5)  1624 (17.7)  1573 (17.2)  1869 (20.4) | 2018 (22.1)  2024 (22.1)  1168 (12.8)  1362 (14.9)  1251 (13.7)  1330 (14.5) |
| Race/ethnicity, n (%)  White, non-Hispanic  Black, non-Hispanic  Other | 8246 (90.1)  340 (3.7)  569 (6.2) | 8479 (92.6)  319 (3.5)  358 (3.9) | 8277 (90.4)  509 (5.6)  367 (4.0) |
| Marital status, n (%)  Married or living as married  Widowed  Divorced or separated  Never married | 6413 (70.1)  1280 (14.0)  1093 (11.9)  369 (4.0) | 6745 (73.7)  1123 (12.3)  1037 (11.3)  251 (2.7) | 6587 (72.0)  1139 (12.4)  1179 (12.9)  248 (2.7) |
| Education, n (%)  Less than high school  High school grad and some college  College graduate  Postgraduate | 422 (4.6)  5548 (60.6)  1572 (17.2)  1613 (17.6) | 455 (5.0)  5883 (64.3)  1515 (16.6)  1303 (14.2) | 679 (7.4)  6161 (67.3)  1236 (13.5)  1077 (11.8) |
| Study center, n (%)  University of Colorado  Georgetown University  Pacific Health Research and Education Institute (Honolulu)  Henry Ford Health System  University of Minnesota  Washington University in St Louis  University of Pittsburgh  University of Utah  Marshfield Clinic Research Foundation  University of Alabama at Birmingham | 628 (6.9)  589 (6.4)  375 (4.1)  1373 (15.0)  1421 (15.5)  1009 (11.0)  1070 (11.7)  1211 (13.2)  1030 (11.3)  449 (4.9) | 601 (6.6)  374 (4.1)  238 (2.6)  1282 (14.0)  1644 (18.0)  1144 (12.5)  1121 (12.2)  1115 (12.2)  1153 (12.6)  484 (5.3) | 549 (6.0)  304 (3.3)  191 (2.1)  1374 (15.0)  1558 (17.0)  1154 (12.6)  1142 (12.5)  979 (10.7)  1337 (14.6)  565 (6.2) |
| Smoking status, n (%)  Never  Former cigarette smoker  Current cigarette smoker | 5580 (61.0)  3051 (33.3)  524 (5.7) | 5346 (58.4)  3141 (34.3)  669 (7.3) | 4761 (52.0)  3168 (34.6)  1224 (13.4) |
| Family history of breast cancer, n (%)  No  Yes  Possibly | 7817 (85.4)  1243 (13.6)  95 (1.0) | 7738 (84.5)  1351 (14.8)  67 (0.7) | 7759 (84.8)  1285 (14.0)  109 (1.2) |
| Age at menarche, n (%)  <10  10-11  12-13  14-15  16+ | 131 (1.4)  1666 (18.2)  4949 (54.1)  1968 (21.5)  441 (4.82) | 135 (1.5)  1672 (18.3)  5079 (55.5)  1926 (21.0)  344 (3.8) | 132 (1.4)  1698 (18.6)  4952 (54.1)  1968 (21.5)  403 (4.4) |
| Age at menopause, n (%)  <40  40-44  45-49  50-54  55+ | 1150 (12.6)  1265 (13.8)  2179 (23.8)  3509 (38.3)  1052 (11.6) | 1210 (13.2)  1261 (13.8)  2107 (23.0)  3542 (38.7)  1036 (11.3) | 1405 (15.4)  1303 (14.2)  2166 (23.7)  3239 (35.4)  1040 (11.4) |
| Number of live births, n (%)  0  1  2  3  4  5 or more | 951 (10.4)  636 (7.0)  2184 (23.9)  2275 (24.9)  1571 (17.2)  1538 (16.8) | 746 (8.2)  647 (7.1)  2169 (23.7)  2350 (25.7)  1598 (17.5)  1646 (18.0) | 750 (8.2)  646 (7.1)  2124 (23.2)  2335 (25.5)  1503 (16.4)  1795 (19.6) |
| Age at first birth, n (%)  Nulliparous  ≤19  20-24  25-29  30-34  ≥35 | 943 (10.3)  1231 (13.5)  4259 (46.5)  2045 (22.3)  506 (5.5)  171 (1.9) | 734 (8.0)  1355 (14.8)  4462 (48.7)  1985 (21.7)  435 (5.0)  167 (1.8) | 739 (8.1)  1888 (20.6)  4376 (47.8)  1582 (17.3)  431 (4.7)  137 (1.5) |
| Postmenopausal hormone use, n (%)  Never / unknown  Former  Current | 2865 (31.3)  1560 (17.0)  4730 (51.7) | 2949 (32.2)  1382 (15.1)  4825 (52.7) | 3054 (33.4)  1477 (16.1)  4622 (50.5) |
| Oral contraceptive use, n (%)  No  Yes | 4614 (50.4)  4541 (49.6) | 4140 (45.2)  5016 (54.8) | 3761 (41.1)  5392 (58.9) |
| Oophorectomy, n (%)  No/ don't know  One ovary  Both ovaries | 7469 (81.6)  569 (6.2)  1117 (12.2) | 7357 (80.4)  560 (6.1)  1239 (13.5) | 7271 (79.4)  608 (6.6)  1274 (13.9) |
| Hysterectomy, n (%)  No/ don't know  Yes | 5943 (64.9)  3212 (35.1) | 5913 (64.6)  3243 (35.4) | 5833 (63.7)  3320 (36.3) |

Supplementary Table S2. Correlation coefficient between daily intakes of CML-AGE (KU/1000kcal) and selected nutrients

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Dietary protein | | | Dietary carbohydrate | Dietary Fructose | Calcium | Dietary MUFA | Dietary PUFA | Dietary SF |
|  | Dairy protein | Animal protein | Plant protein |
| CML-AGE | -0.07 | 0.46 | -0.12 | -0.19 | -0.25 | -0.14 | 0.39 | 0.25 | 0.41 |

Note: All P values are <0.0001

Abbreviations: AGE, advanced glycation end-products; CML, NƐ-carboxymethyl-lysine; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acid, SF: saturated fatty acid

Supplementary Table S3. HRs (95% CI) for tertiles of CML-AGE intake and risk of breast cancer by BMI or fruit and vegetable intake

|  |  |  |  |
| --- | --- | --- | --- |
|  | Tertiles of CML-AGE intake | | |
|  | T1 | T2 | T3 |
| CML-AGE, KU/1000 kcal | 867-4805 | 4806-6638 | 6639-43387 |
| Obesity status | | | |
| Normal weight, 18.5-24.9 kg/m2 (n=10,857) | | | |
| Cases, n | 224 | 211 | 163 |
| HR (95%CI)a | Ref | 1.18 (0.96-1.46) | 1.17 (0.88-1.54) |
| Overweight, 25.0-29.9 kg/m2 (n=9,631) | | | |
| Cases, n | 186 | 194 | 208 |
| HR (95%CI)a | Ref | 0.98 (0.79-1.22) | 1.14 (0.87-1.50) |
| Obese, ≥30 kg/m2 (n=6,689) | | | |
| Cases, n | 80 | 141 | 173 |
| HR (95%CI)a | Ref | 1.31 (0.97-1.75) | 1.32 (0.93-1.87) |
| Fruit and vegetable intake | | | |
| Low intake, 16-463 g/day (n=9,163) | | | |
| Cases, n | 103 | 177 | 244 |
| HR (95%CI)a | Ref | 1.24 (0.96-1.60) | 1.27 (0.95-1.71) |
| Medium intake, 464-686 g/day (n=9,162) | | | |
| Cases, n | 159 | 196 | 177 |
| HR (95%CI)a | Ref | 1.04 (0.82-1.30) | 1.02 (0.76-1.36) |
| High intake, 687-3142 g/day (n=9,139) | | | |
| Cases, n | 232 | 179 | 125 |
| HR (95%CI)a | Ref | 1.20 (0.96-1.50) | 1.36 (1.00-1.85) |

Abbreviations: AGE, advanced glycation end-products; CML, NƐ-carboxymethyl-lysine

aAdjusted for covariates age, energy intake, alcohol, BMI, vigorous activity, race, marital status, education, study center, smoking status, family history, age at menarche, age at menopause, age at first birth, no. of live birth, PMH use, OC use, oophorectomy, hysterectomy, dietary intake of total fat and red meat

Supplementary Table S4. HRs (95% CI) for quintiles of CML-AGE intake and breast cancer risk excluding women diagnosed with breast cancer less than two years after enrollment into the PLCO.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Quintiles of CML-AGE intake | | | | | P-trend |
|  | Q1 | Q2 | Q3 | Q4 | Q5 |
| Cases, n | 230 | 267 | 279 | 270 | 267 |  |
| CML-AGE, KU/1000 kcal | 867-4056 | 4057-5136 | 5137-6208 | 6209-7731 | 7732-43387 |  |
| HR (95%CI)a | Ref | 1.17 (0.98-1.40) | 1.23 (1.03-1.47) | 1.23 (1.03-1.47) | 1.26 (1.04-1.51) | 0.03 |
| HR (95%CI)b | Ref | 1.20 (1.00-1.45) | 1.28 (1.06-1.56) | 1.31 (1.06-1.62) | 1.37 (1.07-1.76) | 0.03 |

Abbreviations: AGE, advanced glycation end-products; CML, NƐ-carboxymethyl-lysine

aAdjusted for covariates age, energy intake, alcohol, BMI, vigorous activity, race, marital status, education, study center, smoking status, family history, age at menarche, age at menopause, age at first birth, no. of live birth, PMH use, OC use, oophorectomy, hysterectomy

bAdjusted for all covariates in a and dietary intake of total fat and red meat

**Supplementary Figure S1. Flow chart for participants in the PLCO**

**Initial Sample size**

**N=(78,215)**

Control arm (n=39,111)

Intervention arm (n=39,104)

Exclusions (n=10,724)

* Personal history of any cancer prior to trial (n=2,306)
* Incomplete BQ & DQX, not cancer free at baseline, without follow-up time (n=8,418)

N=28,380

Missing information on covariates (n=916)

* BMI (n=253)
* Age at menopause (n=200)
* Use of OC (n=13)
* Age at menarche (n=19)
* Family history of BrCa (n=171)
* Use of PMH (n=14)
* Oophorectomy (n=3)
* Hysterectomy (n=4)
* No. of pregnancies (n=39)
* No. of live births (n=2)
* Education (n=13)
* Marital status (n=7)
* Age at first birth (n=67)
* Vigorous activity (n=111)

**N=27,464**

Cases (n=1,592)

* In situ (n=327)
* Invasive (n=1,265)

Missing breast cancer hormone receptor information (n=378)

**N=27,086**

Cases (n=1,214)