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 (%)NoYes | 8661 (94.6)494 (5.4) | 8604 (94.0)552 (6.0) | 8607 (94.0)546 (6.0) |
| BMI (kg/m2), n (%)< 18.518.5- < 2525- < 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-HispanicBlack, non-HispanicOther | 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 schoolHigh school grad and some collegeCollege graduatePostgraduate | 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 ColoradoGeorgetown UniversityPacific Health Research and Education Institute (Honolulu)Henry Ford Health SystemUniversity of MinnesotaWashington University in St LouisUniversity of PittsburghUniversity of UtahMarshfield Clinic Research FoundationUniversity 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 smokerCurrent 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 (%)NoYes 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 (%)<1010-1112-1314-1516+ | 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 (%)<4040-4445-4950-5455+ | 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 (%)012345 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≤1920-2425-2930-34≥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 / unknownFormer 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 (%)NoYes | 4614 (50.4)4541 (49.6) | 4140 (45.2)5016 (54.8) | 3761 (41.1)5392 (58.9) |
| Oophorectomy, n (%)No/ don't knowOne 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 knowYes | 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)