# **Supplementary material**

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| ***Supplemental Table 1:*** *Characteristics of women and men diagnosed with colorectal cancer; for all and according to event (all-cause mortality and colorectal cancer-specific mortality). Characteristics are from recruitment (before diagnosis) and at time of diagnosis. The Diet, Cancer and Health cohort* |
|  | **Women (n=416)** | **Men (n=537)** |
|   | All (n=416) | Event (deceased) | All (n=537) | Event (deceased) |
|   | All-causes (n=210) | Colorectal cancer (n=170) | Non-CRC mortality (n=40) | All-causes (n=325) | Colorectal cancer (n=215) | Non-CRC mortality (n=110) |
|   | Median or n | P5-P95 or %  | Median or n | P5-P95 or %  | Median or n | P5-P95 or %  | Median or n | P5-P95 or %  | Median or n | P5-P95 or %  | Median or n | P5-P95 or %  | Median or n | P5-P95 or %  | Median or n | P5-P95 or %  |
| ***Follow-up***  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Follow-up time used in study (time from diagnosis until death or censoring) | 7 | 0-18 | 2 | 0-10 | 2 | 0-9 | 5 | 0-11 | 6 | 0-16 | 3 | 0-12 | 2 | 0-8 | 5 | 1-14 |
| ***From time of diagnosis*** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Age at diagnosis, years | 65 | 56-75 | 65 | 57-75 | 65 | 57-75 | 67 | 59-75 | 66 | 57-76 | 66 | 57-75 | 65 | 56-75 | 67 | 59-76 |
| **Colorectal cancer subtypes**  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  Proximal colon cancer | 124 | 30% | 59 | 28% | 50 | 29% | 9 | 23% | 122 | 23% | 65 | 20% | 45 | 21% | 20 | 18% |
|  Distal colon cancer | 124 | 30% | 58 | 28% | 48 | 28% | 10 | 25% | 152 | 28% | 91 | 28% | 62 | 29% | 29 | 26% |
|  Rectosigmoid junction | 19 | 5% | 12 | 6% | 12 | 7% | 0 | 0% | 29 | 5% | 23 | 7% | 15 | 7% | 8 | 7% |
|  Rectum | 128 | 31% | 66 | 31% | 49 | 29% | 17 | 43% | 216 | 40% | 130 | 40% | 81 | 38% | 49 | 45% |
|  Overlapping and unspecified | 21 | 5% | 15 | 7% | 11 | 6% | 4 | 10% | 18 | 3% | 16 | 5% | 12 | 6% | 4 | 4% |
| **UICC stage**\***,**† |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  Stage I (T1 or T2, N0, M0) | *38* | *14%* | *8* | *7%* | 3 | 3% | 5 | *13%* | *69* | *18%* | *18* | *9%* | *3* | *2%* | *15* | *14%* |
|  Stage II (T3 or T4, N0, Mo) | 81 | 31% | 17 | 14% | 9 | 9% | 8 | 20% | 123 | 32% | 46 | 22% | 21 | 16% | 25 | 23% |
|  Stage III (any T stage, N1 or N2, Mo) | 77 | 29% | 38 | 31% | 30 | 30% | 8 | 20% | 105 | 28% | 64 | 31% | 37 | 28% | 27 | 25% |
|  Stage IV (M1) | 68 | 26% | 60 | 49% | 57 | 58% | 3 | 8% | 82 | 22% | 78 | 38% | 69 | 53% | 9 | 8% |
| **Charlson Comorbidity Index**\* |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  0 | 228 | 82% | 102 | 77% | 85 | 81% | 17 | 43% | 308 | 78% | 161 | 74% | 111 | 82% | 50 | 45% |
|  1 | *29* | *10%* | *15* | *11%* | 12 | 11% | 3 | *8%* | *48* | *12%* | 30 | 14% | 14 | 10% | 16 | 15% |
|  ≥2 | 21 | 8% | 15 | 11% | 8 | 8% | 7 | 18% | 38 | 10% | 26 | 12% | 11 | 8% | 15 | 14% |
| **ASA Score**\***,**‡ |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  I (normal healthy patient) | *79* | *31%* | *27* | *24%* | 22 | 25% | 5 | *13%* | *106* | *29%* | 42 | 21% | 27 | 22% | 15 | 14% |
|  II (patient with mild systemic disease) | 142 | 56% | 66 | 58% | 54 | 61% | 12 | 30% | 193 | 53% | 104 | 53% | 65 | 53% | 39 | 35% |
|  III (patient with severe systemic disease) | 27 | 11% | 18 | 16% | 13|| | 15%|| | 8|| | 20%|| | 54 | 15% | 43 | 22% | 25 | 20% | 18 | 16% |
|  IV (patient with severe systemic disease that is a constant threat to life) | 4 | 2% | 3 | 3% | 11 | 3% | 9 | 5% | 5 | 4% | 4 | 4% |
| **Radical (curative) surgery**\***,**§ |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  Radical surgery performed | 193 | 71% | 60 | 47% | 38 | 38% | 22 | 85% | 272 | 72% | 115 | 56% | 50 | 39% | 65 | 83% |
|  Radical surgery not performed | 78 | 29% | 67 | 53% | 63 | 62% | 4 | 15% | 107 | 28% | 92 | 44% | 79 | 61% | 13 | 17% |
| ***From recruitment (pre-diagnosis)*** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| BMI, kg/m2 | 26 | 20-36 | 26 | 19-37 | 26 | 20-36 | 27 | 18-38 | 27 | 21-34 | 27 | 21-34 | 27 | 22-33 | 27 | 21-36 |
| BMI group, kg/m2 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  BMI ≤25 | 181 | 44% | 79 | 38% | 64 | 38% | 15 | 38% | 185 | 34% | 111 | 34% | 80 | 37% | 31 | 28% |
|  BMI >25 to ≤30 | 150 | 36% | 83 | 40% | 71 | 42% | 12 | 30% | 264 | 49% | 158 | 49% | 103 | 48% | 55 | 50% |
|  BMI >30 | 85 | 20% | 48 | 23% | 35 | 21% | 13 | 33% | 88 | 16% | 56 | 17% | 32 | 15% | 24 | 22% |
| Menopausal status |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  Pre-menopausal | 48 | 12% | 17 | 8% | 15 | 9% | 2 | 5% | - | - | - | - | - | - | - | - |
|  Post-menopausal | 368 | 88% | 193 | 92% | 155 | 91% | 38 | 95% | - | - | - | - | - | - | - | - |
| Use of hormones |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  Never | 252 | 61% | 136 | 65% | 108 | 64% | 28 | 70% | - | - | - | - | - | - | - | - |
|  Former | 55 | 13% | 24 | 11% | 22 | 13% | 2 | 5% | - | - | - | - | - | - | - | - |
|  Current | 109 | 26% | 50 | 24% | 40 | 24% | 10 | 25% | - | - | - | - | - | - | - | - |
| Schooling |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  Short (≤7 years) | 159 | 38% | 89 | 42% | 65 | 38% | 24 | 60% | 181 | 34% | 110 | 34% | 70 | 33% | 40 | 36% |
|  Medium (8–10 years) | 185 | 44% | 94 | 45% | 80 | 47% | 14 | 35% | 244 | 45% | 148 | 46% | 102 | 47% | 46 | 42% |
|  Long (≥11 years) | 72 | 17% | 27 | 13% | 25 | 15% | 2 | 5% | 112 | 21% | 67 | 21% | 43 | 20% | 24 | 22% |
| Participate in sports (yes) | 215 | 52% | 94 | 45% | 82 | 48% | 12 | 30% | 235 | 44% | 130 | 40% | 89 | 41% | 41 | 37% |
| Smoking status |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  Never | 176 | 42% | 83 | 40% | 64 | 38% | 19 | 48% | 107 | 20% | 56 | 17% | 40 | 19% | 16 | 15% |
|  Former | 93 | 22% | 42 | 20% | 38 | 22% | 4 | 10% | 199 | 37% | 111 | 34% | 75 | 35% | 36 | 33% |
|  Current | 147 | 35% | 85 | 40% | 68 | 40% | 17 | 43% | 231 | 43% | 158 | 49% | 100 | 47% | 58 | 53% |
| Packyears (for current and former smokers) | 18 | 2-41 | 22 | 3-44 | 20 | 3-44 | 30 | 11-41 | 29 | 4-78 | 31 | 5-83 | 29 | 5-78 | 35 | 6-100 |
| Alcohol intake |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  Intake among users, g/day | 9 | 1-42 | 8 | 0-41 | 8 | 0-41 | 3 | 0-40 | 23 | 3-86 | 25 | 3-91 | 23 | 3-90 | 30 | 3-93 |
| Frequency of bowel movements |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  ≤ 4 times/week | 49 | 12% | 29 | 14% | 25 | 15% | 4 | 10% | 20 | 4% | 10 | 3% | 6 | 3% | 10|| | 9%|| |
|  5–6 times/week | 34 | 8% | 11 | 5% | 10 | 6% | 31|| | 78%|| | 31 | 6% | 22 | 7% | 16 | 7% |
|  1 time/day | 269 | 65% | 143 | 68% | 113 | 66% | 308 | 57% | 175 | 54% | 118 | 55% | 57 | 52% |
|  ≥2 times/day | 64 | 15% | 27 | 13% | 22 | 13% | 5 | 13% | 178 | 33% | 118 | 36% | 75 | 35% | 43 | 39% |
| Dietary fiber intake, g/day | 19 | 10-33 | 19 | 9-33 | 19 | 9-32 | 17 | 8-35 | 21 | 11-33 | 20 | 11-33 | 20 | 11-33 | 19 | 11-33 |
| Whole-grain intake, g/day | 34 | 10-76 | 34 | 9-70 | 33 | 9-70 | 36 | 8-71 | 40 | 13-86 | 40 | 13-86 | 40 | 13-81 | 39 | 15-94 |
| Processed meat intake, g/day | 19 | 4-49 | 21 | 4-51 | 21 | 5-48 | 20 | 2-55 | 34 | 9-91 | 35 | 9-92 | 20 | 9-99 | 38 | 11-83 |
| Total plasma enterolactone, nmol/L | 19 | 2-83 | 17 | 2-69 | 16 | 2-70 | 18 | 4-65 | 18 | 3-90 | 18 | 3-79 | 18 | 4-79 | 17 | 2-89 |
| ***From 0-12 months before blood sampling (recruitment, pre-diagnosis)*** |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Antibiotics use |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  0-3 months before recruitment | 29 | 13% | 11 | 10% | 7 | 8% | 4 | 18% | 19 | 6% | 9 | 5% | 4 | 3% | 5 | 8% |
|  3-12 months before recruitment | 46 | 21% | 25 | 23% | 20 | 23% | 5 | 23% | 44 | 15% | 23 | 13% | 13 | 11% | 10 | 17% |
|  No antibiotics use 0-12 months before recruitment | 146 | 66% | 72 | 67% | 59 | 69% | 13 | 59% | 239 | 79% | 148 | 82% | 103 | 86% | 45 | 75% |
| Missing (recruited before 1996 - no register data available) | 195 | 47% | 102 | 49% | 84 | 49% | 16 | 45% | 235 | 44% | 145 | 45% | 95 | 44% | 50 | 45% |
| \**n,women=138 (33%) and n, men=138 (33%) have missing information due to diagnosis before May 2001* †*n,women=14 (3%) and n, men=15 (3%) missing (unknown reason)*‡*n,women=26 (6%) and n, men=30 (6%) missing (unknown reason)*§*n,women=7 (2%) and n, men=15 (3%) missing (unknown reason)*||*Two categories merged into one due to n<3 in one of the categories*¶*includes overlapping and unspecified lesions, and cancers of the rectosigmoid junction* |

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| ***Supplementary Table 2:*** *Sensitivity analyses*\* *with adjustment for general health at time of diagnosis and treatment of the association between pre-diagnosis plasma concentrations of enterolactone as continuous (per doubling in concentration) and risk of all-cause mortality - women and men diagnosed with colorectal cancer from the Diet, Cancer and Health cohort*† |
|   | Women (n=249) | Men (n=355) |
|   | All-cause mortality(n=111) | All-cause mortality(n=192) |
|   | HR | 95% CI | HR | 95% CI |
| Model 1b|| | 0.91 | 0.80;1.04 | 1.04 | 0.95;1.15 |
| Model 1b|| + ASA Score | 0.87 | 0.76;0.99 | 1.03 | 0.94;1.13 |
| Model 1b|| + Charlson Comorbidity Index | 0.93 | 0.82;1.06 | 1.05 | 0.96;1.16 |
| Model 1b|| + Radical (curative) surgery | 0.95 | 0.82;1.09 | 1.06 | 0.96;1.16 |
|   |   |   |   |   |
| *HR, hazard ratio; Q, quartile; CI, confidence interval* \**Sensitivity analyses were made for those with diagnosis after May 2001, because data on general health only was available for this subset (249 of 416 women, 355 of 537 men)*†*Hazard ratios (HR) and 95%CI were obtained by the Cox Proportional Hazards Model*‡*Enterolactone concentrations are expressed in nmol/L*||*All analyses adjusted for age, smoking status (current, former, never), schooling (as measure of socio-economic status, ≤7 years, 8-10 years, ≥11 years), quantification of cigarette smoking i.e. pack-years, waist circumference (cm), alcohol intake (abstainer yes/no, continuous intake), intake of processed meat (g/day), and frequency of bowel movements (*≤*4 times/week, 5–6 times per week, 1 time/day, ≥2 times/day) (≤4 times/week, 5–6 times per week, 1 time/day, ≥2 times/day)* |

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| ***Supplementary Table 3:*** *Analyses by time between blood sample (enterolactone measurement) and diagnosis of the association between pre-diagnosis enterolactone (per doubling in concentration) and risk of all-cause mortality. Women and men diagnosed with colorectal cancer from the Diet, Cancer and Health cohort\** |
|   | Women (n=416) | Men (n=537) |
|   | All-cause mortality(n=210) | All-cause mortality(n=325) |
|   | n (events) | HR | 95% CI | p-value for interaction | n (events) | HR | 95% CI | p-value for interaction |
| ***Continuous, per doubling in concentration***† |
|  **0–5 years**  between blood sample and diagnosis‡ | 120 (67) | 0.90 | 0.78;1.04 | 0.92 | 126 (98) | 1.15 | 1.00;1.32 | 0.0513 |
|  **0–10 years** between blood sample and diagnosis‡ | 139 (76) | 0.92 | 0.83;1.01 | 199 (113) | 1.03 | 0.94;1.12 |
|  **>10 years** between blood sample and diagnosis‡ | 157 (67) | 0.91 | 0.79;1.05 | 212 (114) | 1.04 | 0.93;1.16 |
| *HR, hazard ratio; Q, quartile; CI, confidence interval* \**Hazard ratios (HR) and 95%CI were obtained by the Cox Proportional Hazards Model*†*Enterolactone concentrations are expressed in nmol/L*‡*All analyses adjusted for age, smoking status (current, former, never), schooling (as measure of socio-economic status, ≤7 years, 8-10 years, ≥11 years), quantification of cigarette smoking i.e. pack-years, waist circumference (cm), alcohol intake (abstainer yes/no, continuous intake), intake of processed meat (g/day), and frequency of bowel movements (*≤*4 times/week, 5–6 times per week, 1 time/day, ≥2 times/day)* |

# Supplementary Figures

**Supplementary Figure 1**: Flow-chart
DCCG, Danish Colorectal Cancer Group