Supplemental Table 1. Comparison of sociodemographic and exposure characteristics between participants with both adipose tissue POPs and oxidative stress (OS) biomarkers (n=247) and those with POPs but without OS (n=101).

|                          | POPs + OS (n=247) | Only POPs (n=101) | P-value * |
|--------------------------|-------------------|-------------------|-----------|
| n                        | %                 | n                 | %         |           |
| Sex= male                | 134 (54.3)        | 41 (40.6)         | 0.018     |
| Education                |                   |                   | 0.327     |
| Primary uncompleted       | 67 (27.1)         | 28 (27.7)         |           |
| Primary                  | 116 (47.0)        | 39 (38.6)         |           |
| Secondary or higher      | 64 (25.9)         | 34 (33.7)         |           |
| Residence                |                   |                   | 0.638     |
| Urban                    | 129 (52.2)        | 50 (49.5)         |           |
| Semi-rural               | 118 (47.8)        | 51 (50.5)         |           |
| Alcohol consumer (=yes)  | 126 (51.0)        | 55 (54.5)         | 0.724     |
| Smoker (=yes)            | 79 (40.0)         | 34 (33.7)         | 0.900     |
| Median (P25, P75)        |                   |                   |           |
| Age (years)              | 51.0 (35.0, 64.0) | 50.0 (37.5, 59.0) | 0.338     |
| BMI (kg/m²)              | 27.1 (23.9, 29.8) | 25.7 (23.7, 28.0) | 0.034     |
| PCB-138 (ng/g)           | 82.4 (35.2, 138.7)| 80.7 (3.82, 132.4)| 0.323     |
| PCB-153 (ng/g)           | 216.9 (142.7, 356.2)| 225.7 (105.4, 389.4)| 0.764     |
| PCB-180 (ng/g)           | 179.8 (107.8, 284.3)| 173.0 (82.5, 301.9)| 0.513     |
| p,p′-DDE (ng/g)          | 96.4 (36.0, 211.9) | 87.9 (27.9, 211.1) | 0.523     |
| HCB (ng/g)               | 14.0 (5.41, 40.1) | 15.7 (4.53, 36.4) | 0.633     |
| β-HCH (ng/g)             | 10.0 (4.14, 21.3) | 11.6 (1.35, 20.7) | 0.978     |
| P-value *                |                   |                   |           |
| Dicofol (>LOD)           | 52 (21.1)         | 19 (18.8)         | 0.842     |
| α-HCH (>LOD)             | 51 (20.7)         | 19 (18.8)         | 0.769     |

* P-value for the comparison between cancer and non-cancer cases. Fisher’s exact test and Mann-Whitney’s U for categorical and continuous variables, respectively.
Supplemental Table 2. Localization and classification of benign tumors.

|                      | ICD-10 | n  | n %  |
|----------------------|--------|----|------|
| **Non Hormone-dependent** |        |    |      |
| Skin                 | D23    | 8  | 30.77% |
| Peripheral nerves    | D48    | 2  | 7.69%  |
| Nasopharynx          | D10    | 2  | 7.69%  |
| Pancreas             | D13    | 1  | 3.85%  |
| Soft tissues         | D21    | 1  | 3.85%  |
| Eye                  | D31    | 1  | 3.85%  |
| Hematological        | D47    | 1  | 3.85%  |
| **Hormone-dependent** |        |    |      |
| Breast               | N60    | 3  | 11.54% |
| Prostate             | N40    | 3  | 11.54% |
| Uterus body          | D25    | 2  | 7.69%  |
| Ovary                | N80    | 2  | 7.69%  |
| **Total number of benign tumors** | 26   |    | 100%  |
Supplemental Table 3. Sex-stratified descriptive analysis of sociodemographic characteristics and adipose tissue POP concentrations (n=348).

|                          | Men (n=175) | Women (n=173) | P-value * |
|--------------------------|-------------|---------------|-----------|
|                          | n   | %   | n   | %   |           |
| Education                |     |     |     |     |           |
| Primary uncompleted      | 49  | 28.0| 46  | 26.6| 0.533     |
| Primary                  | 73  | 41.7| 82  | 47.4|           |
| Secondary or higher      | 53  | 30.3| 45  | 26.0|           |
| Residence                |     |     |     |     |           |
| Urban                    | 100 | 57.1| 79  | 45.7| 0.041     |
| Semi-rural               | 75  | 42.9| 94  | 54.3|           |
| Alcohol consumer (=yes)  | 132 | 75.4| 49  | 28.3| <0.001    |
| Smoker (=yes)            | 75  | 42.9| 38  | 22.0| <0.001    |
| Age (years)              |     |     |     |     | 0.874     |
| BMI (kg/m²)              | 26.8| 29.1| 26.2| 29.8| 0.401     |
| PCB-138 (ng/g)           | 72.9| 123.3| 86.4| 147.5| 0.206     |
| PCB-153 (ng/g)           | 210.7| 337.9| 234.5| 383.0| 0.412     |
| PCB-180 (ng/g)           | 179.0| 309.4| 177.2| 291.7| 0.750     |
| p,p′-DDE (ng/g)          | 70.2| 175.7| 114.0| 283.1| <0.001    |
| HCB (ng/g)               | 9.4 | 24.2| 28.4| 53.3| <0.001    |
| β-HCH (ng/g)             | 7.3 | 14.5| 15.3| 30.0| <0.001    |
| Dicofol (>LOD)           | 36  | 20.6| 35  | 20.2| 1.000     |
| α-HCH (>LOD)             | 20  | 11.4| 50  | 28.9| <0.001    |

* P-value for the comparison between cancer and non-cancer cases. Fisher’s exact test and Mann-Whitney’s U for categorical and continuous variables, respectively.
Supplemental Table 4. Sex-stratified descriptive analysis of oxidative stress biomarkers (n=247).

|                      | Men (n=134)          | Women (n=113)         | P-value $^a$ |
|----------------------|----------------------|-----------------------|--------------|
|                      | Median (P25, P75)    | Median (P25, P75)     |              |
| TBARS (µM)           | 2.70 (1.58, 7.37)    | 3.78 (1.88, 7.98)     | 0.178        |
| SOD (U/mL)           | 8.53 (3.95, 17.2)    | 9.18 (4.93, 15.6)     | 0.720        |
| HO-1 (ng/ml)         | 18.9 (8.24, 24.5)    | 13.7 (5.90, 23.9)     | 0.112        |
| GPx (U/mL)           | 11.8 (9.13, 17.1)    | 11.2 (8.23, 16.8)     | 0.453        |
| GRd (U/mL)           | 0.09 (0.04, 0.16)    | 0.11 (0.06, 0.18)     | 0.120        |
| Total glutathione (nmol/ml) | 16.3 (3.20, 31.2) | 18.9 (4.90, 35.9)     | 0.461        |
| GSSG (nmol/ml)       | 0.34 (0.01, 8.15)    | 3.08 (0.01, 15.0)     | 0.037        |
| GSH (nmol/ml)        | 9.47 (2.95, 24.5)    | 7.54 (1.86, 20.5)     | 0.394        |
| GSSG/GSH             | 0.28 (0.01, 1.00)    | 0.64 (0.03, 1.23)     | 0.006        |
| 8OHdG b (ng/ml)      | 0.45 (0.09, 1.40)    | 0.75 (0.25, 2.34)     | 0.079        |

Data are presented as median (percentile 25, percentile 75). Oxidative biomarkers: thiobarbituric acid reactive substances (TBARS); superoxide dismutase (SOD); heme oxygenase-1 (HO-1); glutathione peroxidase (GPx); glutathione reductase (GRd); oxidized glutathione (GSSG); reduced glutathione (GSH), 8-hydroxydeoxyguanosine (8OHdG).

$^a$ P-value for the comparison between cancer and non-cancer cases using Mann-Whitney’s U test.

$^b$ Measurement only available in 209 study participants (113 men and 96 women).
Supplemental Table 5. Sex-stratified Cox-regression analyses showing longitudinal associations between adipose tissue levels of persistent organic pollutants and the 16-year incidence of total and non-hormone dependent cancers in GraMo cohort (n=348).

| POPs  | Total cancer incidence a/c | NHD cancers b/d |
|-------|-----------------------------|-----------------|
|       | HR (95% CI) | p-value | n/N | HR (95% CI) | p-value | n/N |
| PCB-138 | 2.05 (1.05, 4.00) | 0.035 | 21/152 | 2.05 (0.76, 5.55) | 0.159 | 10/152 |
| PCB-153 | 2.02 (0.93, 4.30) | 0.075 | 21/152 | 2.14 (0.69, 6.69) | 0.189 | 10/152 |
| PCB-180 | 2.21 (1.03, 4.71) | 0.041 | 21/152 | 1.76 (0.62, 4.98) | 0.284 | 10/152 |
| p,p'-DDE | 1.40 (0.91, 2.16) | 0.126 | 21/152 | 1.71 (0.85, 3.45) | 0.130 | 10/152 |
| HCB     | 1.59 (0.95, 2.66) | 0.080 | 21/152 | 1.79 (0.81, 3.93) | 0.148 | 10/152 |
| β-HCH   | 1.34 (0.82, 2.20) | 0.247 | 21/152 | 1.73 (0.68, 4.39) | 0.249 | 10/152 |
| α-HCH   | 1.39 (0.43, 4.53) | 0.588 | 21/152 | 4.39 (0.60, 32.2) | 0.146 | 10/152 |
| Dicofol | 0.46 (0.10, 2.13) | 0.322 | 21/152 | 0.51 (0.05, 4.80) | 0.556 | 10/152 |

| POPs  | Men (n=175) | Total cancer incidence a/c | NHD cancers b/d |
|-------|-------------|-----------------------------|-----------------|
|       | HR (95% CI) | p-value | n/N | HR (95% CI) | p-value | n/N |
| PCB-138 | 1.15 (0.84, 1.58) | 0.392 | 23/152 | 1.62 (0.85, 3.07) | 0.142 | 17/152 |
| PCB-153 | 0.92 (0.64, 1.34) | 0.670 | 23/152 | 1.42 (0.60, 3.36) | 0.427 | 17/152 |
| PCB-180 | 0.94 (0.64, 1.38) | 0.759 | 23/152 | 1.15 (0.53, 2.49) | 0.723 | 17/152 |
| p,p'-DDE | 1.18 (0.80, 1.75) | 0.404 | 23/152 | 1.21 (0.77, 1.92) | 0.408 | 17/152 |
| HCB     | 1.14 (0.81, 1.62) | 0.458 | 23/152 | 1.64 (1.00, 2.69) | 0.052 | 17/152 |
| β-HCH   | 1.40 (0.97, 2.03) | 0.074 | 23/152 | 1.75 (1.08, 2.84) | 0.023 | 17/152 |
| α-HCH   | 2.35 (0.61, 9.14) | 0.217 | 23/152 | 1.55 (0.27, 9.02) | 0.628 | 17/152 |
| Dicofol | 0.75 (0.24, 2.36) | 0.622 | 23/152 | 1.56 (0.45, 5.43) | 0.486 | 17/152 |

Data are presented as Hazard Ratio and 95% Confidence Intervals [HR (95% CIs)]. Models were adjusted for age (years), sex (male/female), BMI (kg/m²), smoking (yes/no), alcohol consumption (yes/no), place of residence (urban vs. semi-rural) and education (lower than primary education, primary education or higher than primary).

* Female incident cases of total cancer (n=21) excluding benign tumors and basal cell carcinomas (BCCs). Rest of the study population (n=152).
* Non-hormone dependent (NHD) cancers (n=10), excluding hormone-dependent (HD) cancers (n=11). Rest of the study population (n=152).
* Male incident cases of total cancer (n=23) excluding benign tumors and basal cell carcinomas (BCCs). Rest of the study population (n=152).
* Non-hormone dependent (NHD) cancers (n=17) excluding hormone-dependent (HD) cancers (n=6). Rest of the study population (n=152).
Supplemental Table 6. Cox-regression analyses showing longitudinal associations between adipose tissue levels of persistent organic pollutants and the 16-year cancer incidence in GraMo cohort, without adjustment for BMI (n=348).

| POPs   | Total cancer incidence a | NHD cancers b |
|--------|--------------------------|---------------|
|        | HR (95% CI) p-value n/N  | HR (95% CI) p-value n/N |
| PCB-138 | 1.40 (1.03, 1.92) 0.034 44/304 | 1.97 (1.12, 3.46) 0.019 27/304 |
| PCB-153 | 1.25 (0.86, 1.80) 0.244 44/304 | 2.03 (1.03, 4.00) 0.040 27/304 |
| PCB-180 | 1.30 (0.91, 1.87) 0.148 44/304 | 1.65 (0.87, 3.12) 0.124 27/304 |
| p,p’-DDE | 1.35 (1.01, 1.78) 0.040 44/304 | 1.49 (1.03, 2.14) 0.034 27/304 |
| HCB     | 1.31 (1.00, 1.72) 0.052 44/304 | 1.65 (1.11, 2.45) 0.014 27/304 |
| β-HCH   | 1.39 (1.04, 1.86) 0.027 44/304 | 1.79 (1.17, 2.74) 0.008 27/304 |
| α-HCH c | 1.77 (0.75, 4.20) 0.196 44/304 | 3.01 (0.96, 9.39) 0.058 27/304 |
| Dicofol c | 0.70 (0.30, 1.61) 0.397 44/304 | 1.26 (0.46, 3.46) 0.763 27/304 |

Data are presented as Hazard Ratio and 95% Confidence Intervals [HR (95% CIs)]. Models were adjusted for age (years), sex (male/female), smoking (yes/no), alcohol consumption (yes/no), place of residence (urban vs. semi-rural) and education (lower than primary education, primary education or higher than primary).

a All incident cases of cancer (n=44), excluding benign tumors and basal cell carcinomas (BCCs). Rest of the study population (n=304).

b Non-hormone dependent (NHD) cancers (n=27), excluding hormone-dependent (HD) cancers (n=17). Rest of the study population (n=304).

c Participants with concentrations above the limit of detection were compared to those with non-detected concentrations.
Supplemental Table 7. Mediation analysis. Effect estimates (95% CIs) of each natural log-unit increase in adipose tissue POP concentrations and the estimated percentage mediated by selected in situ oxidative stress biomarkers on the risk of non-hormone dependent cancers, without adjustment for BMI (n=247).

| Oxidative Stress marker | POPs | Indirect effect HR (95% CI) \(^a\) | Direct effect HR (95% CI) \(^a\) | Total effect HR (95% CI) \(^a\) | Estimated percent mediated (%) \(^b\) |
|-------------------------|------|----------------------------------|---------------------------------|---------------------------------|----------------------------------|
| SOD                     | HCB  | 1.11 (0.87, 1.40)                | 1.19 (1.07, 1.35)               | 1.31 (1.07, 1.60)               | 39                               |
|                         | β-HCH| 1.14 (0.91, 1.44)                | 1.28 (1.14, 1.51)               | 1.47 (1.17, 1.81)               | 34                               |
|                         | PCB-138| 1.09 (0.79, 1.46)              | 1.61 (1.28, 1.96)               | 1.76 (1.26, 1.96)               | 15                               |
| GRd                     | HCB  | 1.05 (0.83, 1.33)                | 1.28 (1.14, 1.52)               | 1.35 (1.11, 1.65)               | 16                               |
|                         | β-HCH| 1.16 (0.92, 1.48)                | 1.24 (1.10, 1.45)               | 1.44 (1.15, 1.77)               | 41                               |
|                         | PCB-138| 1.14 (0.83, 1.56)              | 1.49 (1.24, 1.89)               | 1.70(1.22, 2.05)                | 25                               |

Non-hormone dependent (NHD) cancers (n=17), excluding hormone-dependent cancers (n=6) from the analysis. Rest of the study population (n=224). Superoxide dismutase (SOD); glutathione reductase (GRd). Models were adjusted for age (years), sex (male/female), smoking (yes/no), alcohol consumption (yes/no), place of residence (urban vs. semi-rural) and education (lower than primary education, primary education or higher than primary).

\(^a\) The direct effect, indirect effect, and total effect reflect the natural log Hazard Ratios (HR) and 95% Confidence Intervals (95% CI). The indirect effect represents the mediated effect.

\(^b\) Percent mediated = indirect effect/ (direct effect + indirect effect) × 100.
Supplemental Table 8. Cox-regression analyses showing longitudinal associations between adipose tissue oxidative stress biomarkers and the 16-year cancer incidence in GraMo cohort (n=247), with further adjustment for reason for surgery.

| Biomarker | Total cancer incidence * | NHD cancers b |
|-----------|--------------------------|---------------|
|           | HR (95% CI) | p-value | n/N | HR (95% CI) | p-value | n/N |
| SOD       | 1.36 (0.97, 1.91) | 0.074 | 23/224 | 1.76 (1.16, 2.67) | 0.007 | 17/224 |
| HO-1      | 1.40 (0.82, 2.37) | 0.213 | 23/224 | 1.34 (0.73, 2.45) | 0.340 | 17/224 |
| GPx       | 1.08 (0.67, 1.77) | 0.747 | 23/224 | 1.13 (0.58, 2.19) | 0.720 | 17/224 |
| GRd       | 1.37 (0.92, 2.06) | 0.123 | 23/224 | 2.32 (1.34, 4.02) | 0.003 | 17/224 |
| Total Glutathione | 0.94 (0.83, 1.05) | 0.270 | 23/224 | 0.91 (0.79, 1.05) | 0.188 | 17/224 |
| GSSG      | 0.93 (0.83, 1.04) | 0.228 | 23/224 | 0.87 (0.75, 1.01) | 0.072 | 17/224 |
| GSH       | 0.94 (0.84, 1.05) | 0.258 | 23/224 | 0.92 (0.81, 1.05) | 0.228 | 17/224 |
| GSSG/GSH  | 0.98 (0.88, 1.10) | 0.753 | 23/224 | 0.95 (0.83, 1.09) | 0.439 | 17/224 |
| TBARS     | 1.15 (0.73, 1.79) | 0.549 | 23/224 | 1.37 (0.78, 2.38) | 0.271 | 17/224 |
| 8OHdG c   | 0.94 (0.78, 1.14) | 0.580 | 23/186 | 1.03 (0.80, 1.31) | 0.840 | 17/186 |

Data are presented as Hazard Ratio and 95% Confidence Intervals [HR (95% CIs)]. Models were adjusted for: age (years), sex (male/female), BMI (kg/m²), smoking (yes/no), alcohol consumption (yes/no), place of residence (urban vs. semi-rural), education (lower than primary education, primary education or higher than primary) and reason for surgery (hernias, gallbladder disease, varicose veins and other conditions). Oxidative biomarkers: thiobarbituric acid reactive substances (TBARS); superoxide dismutase (SOD); heme oxygenase (HO-1); glutathione peroxidase (GPx); glutathione reductase (GRd); glutathione S-transferase (GST); oxidized glutathione (GSSG); reduced glutathione (GSH).

* All incident cases of cancer (n=23), excluding benign tumors and basal cell carcinomas (BCCs). Rest of the study population (n=224).

b Non-hormone dependent (NHD) cancers (n=17), excluding hormone-dependent cancers (n=6) from the analysis. Rest of the study population (n=224).

c 8OHdG measures were only available for 209 participants.
Supplemental Table 9. Cox-regression analyses showing longitudinal associations between adipose tissue levels of persistent organic pollutants and the 16-year cancer incidence in GraMo cohort (n=348), with further adjustment for reason for surgery.

| POPs       | Total cancer incidence a | NHD cancers b |
|------------|--------------------------|---------------|
|            | HR (95% CI) p-value n/N  | HR (95% CI) p-value n/N |
| PCB-138    | 1.31 (0.96, 1.79) 0.093 44/304 | 1.73 (0.99, 3.01) 0.053 27/304 |
| PCB-153    | 1.13 (0.79, 1.62) 0.493 44/304 | 1.68 (0.86, 3.29) 0.132 27/304 |
| PCB-180    | 1.23 (0.85, 1.76) 0.274 44/304 | 1.45 (0.78, 2.70) 0.237 27/304 |
| p,p'-DDE   | 1.16 (0.87, 1.56) 0.312 44/304 | 1.31 (0.89, 1.94) 0.172 27/304 |
| HCB        | 1.27 (0.94, 1.71) 0.125 44/304 | 1.54 (1.01, 2.35) 0.045 27/304 |
| β-HCH      | 1.31 (0.97, 1.77) 0.074 44/304 | 1.64 (1.06, 2.54) 0.025 27/304 |
| α-HCH c    | 1.49 (0.62, 3.63) 0.376 44/304 | 2.78 (0.84, 9.25) 0.096 27/304 |
| Dicofol c  | 0.77 (0.32, 1.81) 0.542 44/304 | 1.22 (0.44, 3.39) 0.707 27/304 |

Data are presented as Hazard Ratio and 95% Confidence Intervals [HR (95% CIs)]. Models were adjusted for age (years), sex (male/female), BMI (kg/m²), smoking (yes/no), alcohol consumption (yes/no), place of residence (urban vs. semi-rural), education (lower than primary education, primary education or higher than primary) and reason for surgery (hernias, gallbladder disease, varicose veins and other conditions).

a All incident cases of cancer (n=44), excluding benign tumors and basal cell carcinomas (BCCs). Rest of the study population (n=304).
b Non-hormone dependent (NHD) cancers (n=27), excluding hormone-dependent (HD) cancers (n=17). Rest of the study population (n=304).
c Participants with concentrations above the limit of detection were compared to those with non-detected concentrations.