**Supplementary Table 1.** Summary of Previously Published Prospective Cohort Studies of Circulating CRP and Breast Cancer Risk.

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| --- | --- | --- | --- | --- | --- | --- |
| **Study (First author, year)** | **Study design**  | **No. of cases** | **No. of controls/cohort** | **CRP measurement** | **CRP category cut-offs (mg/L)** | **Analysis/adjusted variables** |
| The Rotterdam Study, Netherlands (Siemes, 2006) | Entire cohort used | 184 | 3790 | High sensitivity near-infrared particle immunoassay | <1, 1-3, 3-10 | Cox proportional hazard models adjusted for age, smoking, body mass index, age at menarche and menopause, hormone use, and number of children. |
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| The New York UniversityWomen’s Health Study, U.S.(Zeleniuch-Jacquotte, 2008) | Nested case-control, post-menopausal women only | 85 | 163 | High sensitivity nephelometric immunoassay  | <0.28, 0.28-0.72,>0.72 | Conditional logistic regression included matching variables age at entry and date of enrollment, and adjusted for percent of sex hormone binding globulin bound estradiol.  |
| The Copenhagen City Heart Study, Denmark (Allin, 2009) | Entire cohort used | 207 | 5561 | High sensitivity turbidimetric or nephelometric immunoassay | <1.12, 1.12 - 1.43, 1.44 - 2.00, 2.01 - 3.67, ≥ 3.68 | Cox proportional hazard models adjusted for age, smoking, alcohol consumption, body mass index, oral contraceptive therapy, menopausal status, and hormone replacement therapy. |
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| The Multi-ethnic Cohort, U.S. (Ollberding, 2013) | Nested case-control, post-menopausal women only | 706 | 706 | High sensitivity immunoturbidimetric assay  | ≤ 0.9, 1.0 - 1.9, 2.0 - 4.0, >4.0 | Conditional logistic regression included matching variables age of birth, location, ethnicity, date of blood draw, time of blood draw, hours fasting before blood draw, and hormone replacement therapy use at blood draw, and adjusted for body mass index.  |
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| The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study, France (Touvier, 2013) | Nested case-control, post-menopausal women only | 218 | 436 | High sensitivity ELISA | <0.5, 0.5 - <0.9, 0.9 - <1.9, ≥1.9 | Conditional logistic regression included matching variables age, body mass index, and SU.VI.MAX intervention group, and adjusted for height, alcohol intake, physical activity, smoking status, educational level, family history of breast cancer, number of children, use of hormone replacement therapy for menopause and menopausal status at baseline, and plasma levels of adiponectin, leptin, soluble intercellular adhesion molecule 1,soluble vascular cell adhesion molecule 1, soluble E-selectin, and monocyte chemoattractant protein 1. |
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**Supplementary Table 1. Cont’d**

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| --- | --- | --- | --- | --- | --- | --- |
| **Study (First author, year)** | **Study design**  | **No. of cases** | **No. of controls/cohort** | **CRP measurement** | **CRP category cut-offs (mg/L)** | **Analysis/adjusted variables** |
| The Cancer Prevention Study-II (CPS-II) Nutrition Cohort, U.S. (Gaudet, 2013) | Nested case-control, post-menopausal women only | 297 | 297 | High sensitivity ELISA | 0.107 - 1.076, >1.076 - 2.669, 2.669 - 28.647 | Conditional logistic regression included matching variables age, race and blood draw date, and adjusted for time from last meal to blood draw, alcohol in the 24 hours before blood draw, prior diagnosis of diabetes, family history of breast cancer, and body mass index. |
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|  |  |  |  |  |  |  |
| The Atherosclerosis Risk in Communities Study (Prizment, 2013) | Entire cohort used | 176 | 7603 | High sensitivityimmunoturbidimetric assay  | <1.09, 1.09-2.44,2.45-5.64, >5.64  | Cox proportional hazard models adjusted for age, study center, education, body mass index, waist, aspirin use, smoking status, pack-years of smoking, hormone therapy use, menopausal status, age at menarche, and number of live births |
| The E3N cohort, France (Dossus, 2014) | Nested case-control, post-menopausal women only | 549 | 1040 | High sensitivity immunoturbidimetric assay | <1.5, 1.5 - <2.5, 2.5 - <10 | Conditional logistic regression included matching variables age at blood collection, menopausal status at blood collection, year of blood collection, center of collection, and age at menopause |
|  |  |  |  |
|  |  |  |  |  |  |
| The Chinese Kailuan Female Cohort (Wang, 2014) | Entire cohort used | 87 | 19437 | High sensitivity nephelometric immunoassay | <1, 1-3, >3 | Cox proportional hazard models adjusted for age, smoking, alcohol consumption, body mass index, diabetes, physical activity and marital status |
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**Supplementary Table 2**. Plasma CRP Levels and Risk of Breast Cancer Overall by Menopausal Status, BMI, Aspirin Use in the NHS and WHS Respectively and the Combined Analysis.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |   |   | **Quintile 1** |  | **Quintile 2** |  | **Quintile 3** |  | **Quintile 4** |  | **Quintile 5** |   | **Trend-test P-value** |
| ***Pre-menopausal*** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | **NHS**  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Co |  | 81|74 |  | 33|48 |  | 37|33 |  | 27|29 |  | 21|23 |  |  |
|  |  RR(95%CI)a |  | 1.00Ref |  | 0.77 (0.43, 1.40) |  | 1.06 (0.56, 2.01) |  | 0.90 (0.45, 1.80) |  | 0.94 (0.42, 2.08) |  | 0.99 |
|  | **WHS** |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Person-years |  | 179|39814 |  | 100|27751 |  | 79|21442 |  | 78|18049 |  | 66|15093 |  |  |
|  |  HR(95%CI)b |  | 1.00Ref |  | 0.81 (0.63, 1.04) |  | 0.81 (0.61, 1.08) |  | 0.92 (0.68, 1.23) |  | 0.99 (0.72, 1.38) |  | 0.61 |
|  | **Combined** |  | 1.00Ref |  | 0.80 (0.63, 1.01) |  | 0.85 (0.65, 1.10) |  | 0.91 (0.70, 1.20) |  | 0.99 (0.73, 1.34) |  | 0.63 |
|  | ***P*-hetc** |   |   |   |   |   |   |   |   |   |   |   | 0.87 |
| ***Post-menopausal*** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | **NHS**  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Co |  | 99|152 |  | 98|181 |  | 111|183 |  | 148|205 |  | 191|201 |  |  |
|  |  RR(95%CI)d |  | 1.00Ref |  | 0.76 (0.53, 1.10) |  | 0.90 (0.63, 1.30) |  | 1.06 (0.74, 1.52) |  | 1.35 (0.94, 1.95) |  | 0.003 |
|  | **WHS** |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Person-years |  | 183|35055 |  | 205|44298 |  | 245|48163 |  | 272|51043 |  | 218|52787 |  |  |
|  |  HR(95%CI)e |  | 1.00Ref |  | 0.89 (0.72, 1.09) |  | 0.98 (0.80, 1.21) |  | 1.02 (0.83, 1.25)  |  | 0.82 (0.65, 1.02) |  | 0.10 |
|  | **Combined** |  | 1.00Ref |  | 0.85 (0.71, 1.02) |  | 0.96 (0.81, 1.15) |  | 1.03 (0.86, 1.23) |  | 1.03 (0.63, 1.69) |  | 0.59 |
|  | ***P*-hetc** |   |   |   |   |   |   |   |   |   |   |   | 0.001 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ***BMI < 25*** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | **NHS**  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Co |  | 156|191 |  | 103|168 |  | 94|124 |  | 88|101 |  | 75|67 |  |  |
|  |  RR(95%CI)f |  | 1.00Ref |  | 0.73 (0.52, 1.04) |  | 0.90 (0.62, 1.31) |  | 1.05 (0.71, 1.56) |  | 1.19 (0.77, 1.84) |  | 0.13 |
|  | **WHS** |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Person-years |  | 317|71560 |  | 248|55315 |  | 187|42273 |  | 174|32806 |  | 102|22035 |  |  |
|  |  HR(95%CI)g |  | 1.00Ref |  | 0.98 (0.83, 1.17) |  | 0.94 (0.78, 1.13) |  | 1.07 (0.88, 1.30) |  | 0.93 (0.73, 1.18) |  | 0.78 |
|  | **Combined** |  | 1.00Ref |  | 0.89 (0.67, 1.17) |  | 0.93 (0.79, 1.10) |  | 1.06 (0.89, 1.27) |  | 0.98 (0.80, 1.21) |  | 0.56 |
|  | ***P*-hetc** |   |   |   |   |   |   |   |   |   |   |   | 0.13 |

**Supplementary Table 2.** Cont'd.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |   |   | **Quintile 1** |  | **Quintile 2** |  | **Quintile 3** |  | **Quintile 4** |  | **Quintile 5** |   | **Trend-test P-value** |
| ***BMI ≥ 25*** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | **NHS**  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Co |  | 36|54 |  | 55|74 |  | 67|119 |  | 112|145 |  | 157|178 |  |  |
|  |  RR(95%CI)h |  | 1.00Ref |  | 1.13 (0.64, 2.00) |  | 0.84 (0.48, 1.46) |  | 1.18 (0.70, 1.99) |  | 1.34 (0.80, 2.25) |  | 0.07 |
|  | **WHS** |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Person-years |  | 84|17451 |  | 116|31904 |  | 197|43748 |  | 247|53127 |  | 247|63645 |  |  |
|  |  HR(95%CI)i |  | 1.00Ref |  | 0.76 (0.57, 1.02) |  | 0.95 (0.73, 1.24) |  | 0.97 (0.75, 1.26) |  | 0.82 (0.63, 1.06) |  | 0.31 |
|  | **Combined** |  | 1.00Ref |  | 0.86 (0.60, 1.22) |  | 0.93 (0.73, 1.18) |  | 1.01 (0.80, 1.27) |  | 0.99 (0.62, 1.59) |  | 0.63 |
|  | ***P*-hetc** |   |   |   |   |   |   |   |   |   |   |   | 0.04 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ***Non-current use of aspirin*** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | **NHS**  |  |  |  |  |  |  |  |  |  |  |  |  |
|  Ca|Co |  | 107|133 |  | 80|124 |  | 88|129 |  | 103|137 |  | 112|126 |  |  |
|  |  RR(95%CI)j |  | 1.00Ref |  | 0.81 (0.54, 1.21) |  | 0.93 (0.62, 1.39) |  | 1.05 (0.70, 1.59) |  | 1.18 (0.77, 1.81) |  | 0.16 |
|  | **WHS** |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Person-years |  | 201|44570 |  | 174|43437 |  | 197|42934 |  | 216|43493 |  | 165|42230 |  |  |
|  |  HR(95%CI)k |  | 1.00Ref |  | 0.91 (0.74, 1.12) |  | 1.05 (0.85, 1.30) |  | 1.09 (0.88, 1.35) |  | 0.89 (0.70, 1.13) |  | 0.44 |
|  | **Combined** |  | 1.00Ref |  | 0.89 (0.73, 1.07) |  | 1.02 (0.85, 1.23) |  | 1.08 (0.89, 1.31) |  | 0.97 (0.75, 1.25) |  | 0.71 |
|  | ***P*-hetc** |   |   |   |   |   |   |   |   |   |   |   | 0.11 |
| ***Current use of aspirin*** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | **NHS**  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Co |  | 85|112 |  | 78|118 |  | 73|114 |  | 97|109 |  | 120|119 |  |  |
|  |  RR(95%CI)j |  | 1.00Ref |  | 0.86 (0.56, 1.31) |  | 0.81 (0.52, 1.27) |  | 1.21 (0.77, 1.89) |  | 1.36 (0.87, 2.13) |  | 0.03 |
|  | **WHS** |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  Ca|Person-years |  | 200|44467 |  | 190|43793 |  | 187|43149 |  | 205|42515 |  | 184|43506 |  |  |
|  |  HR(95%CI)k |  | 1.00Ref |  | 0.92 (0.75, 1.14) |  | 0.91 (0.73, 1.12) |  | 1.02 (0.82, 1.27) |  | 0.90 (0.71, 1.14) |  | 0.64 |
|  | **Combined** |  | 1.00Ref |  | 0.91 (0.76, 1.10) |  | 0.89 (0.73, 1.08) |  | 1.05 (0.87, 1.28) |  | 1.05 (0.71, 1.56) |  | 0.48 |
|  | ***P*-hetc** |   |   |   |   |   |   |   |   |   |   |   | 0.02 |

a Adjusted for age, month of blood collection, time of day of blood draw, fasting status, family history of breast cancer, history of benign breast disease, BMI at blood collection, age at menarche, parity and age at first birth, alcohol intake, smoking, and physical activity.

b Adjusted for age, randomized treatment assignment , family history of breast cancer, history of benign breast disease, BMI at blood collection, age at menarche, parity and age at first birth, alcohol intake, smoking and physical activity.

c P-value for test between study heterogeneity of the trend.

d Adjusted for the same variables in a and PMH use.

e Adjusted for the same variables in b and PMH use.

f Adjusted for age, month of blood collection, time of day of blood draw, fasting status, menopausal status at blood draw and diagnosis, PMH use, family history of breast cancer, history of benign breast disease, BMI at blood collection (<21, 21-<23, 23-<25 kg/m2), age at menarche, parity and age at first birth, alcohol, smoking and physical activity.

g Adjusted for age, randomized treatment assignment, menopausal status and PMH use, family history of breast cancer, history of benign breast disease, BMI at blood collection (<21, 21-<23, 23-<25 kg/m2), age at menarche, parity and age at first birth, alcohol, smoking and physical activity.

h Adjusted for the same variables in f except that BMI was adjusted as 25-<30 or ≥30kg/m2.

i Adjusted for the same variables in g except that BMI was adjusted as 25-<30 or ≥30kg/m2.

j Adjusted for the same variables in a and menopausal status at blood draw and diagnosis and PMH use.

k Adjusted for age, menopausal status and PMH use, family history of breast cancer, history of benign breast disease, BMI at blood collection, age at menarche, parity and age at first birth, alcohol, smoking and physical activity.

**Supplementary Table 3.** Plasma CRP Levels and Risk of Breast Cancer Overall by Years of Follow-up in the NHS and WHS Respectively.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |   |   | **Quintile 1** |  | **Quintile 2** |  | **Quintile 3** |  | **Quintile 4** |  | **Quintile 5** |   | **Trend-test P-value** |
| ***NHS***  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  **Follow-up ≤ 4 yrs** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Ca|Co |  | 74|99 |  | 65|109 |  | 75|102 |  | 101|108 |  | 94|109 |  |  |
|  | RR(95%CI)a |   | 1.00Ref |   | 0.84 (0.52, 1.36) |   | 1.01 (0.62, 1.64) |   | 1.18 (0.74, 1.88) |   | 1.13 (0.68, 1.86) |   | 0.36 |
|  **Follow-up 5-8 yrs** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Ca|Co |  | 118|146 |  | 93|133 |  | 85|139 |  | 99|138 |  | 138|136 |  |  |
|  | RR(95%CI)a |   | 1.00Ref |   | 0.89 (0.61, 1.30) |   | 0.86 (0.57, 1.28) |   | 1.03 (0.68, 1.55) |   | 1.40 (0.93, 2.11) |   | 0.01 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ***WHS*** |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  **Follow-up ≤5 yrs** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Ca|Person-years |  | 106|27898 |  | 101|27445 |  | 113|27282  |  | 125|27463 |  | 77|27510 |  |  |
|  | HR(95%CI)b |   | 1.00Ref |   | 0.95 (0.71, 1.26) |   | 1.08 (0.81, 1.43) |   | 1.23 (0.92, 1.64) |   | 0.75 (0.53, 1.05) |   | 0.10 |
|  **Follow-up 6-10 yrs** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Ca|Person-years |  | 140|26807 |  | 127|26343 |  | 132|26013 |  | 125|26138 |  | 133|26136 |  |  |
|  | HR(95%CI)b |   | 1.00Ref |   | 0.92 (0.71, 1.18) |   | 0.96 (0.75, 1.24) |   | 0.87 (0.66, 1.14) |   | 0.97 (0.74, 1.29) |   | 0.96 |
|  **Follow-up > 10 yrs** |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Ca|Person-years |  | 155|26807 |  | 136|26343 |  | 139|26013 |  | 171|26138 |  | 139|26136 |  |  |
|  | HR(95%CI)b |   | 1.00Ref |   | 0.89 (0.70, 1.13) |   | 0.92 (0.72, 1.17) |   | 1.10 (0.86, 1.41) |   | 0.91 (070, 1.19) |   | 0.91 |

a Adjusted for family history of breast cancer, history of benign breast disease, BMI at blood collection, age at menarche, parity and age at first birth, alcohol, smoking, and physical activity.

b Adjusted for age, randomized treatment assignment, menopausal status and postmenopausal hormone use, family history of breast cancer, history of benign breast disease, BMI at blood collection, age at menarche, parity and age at first birth, alcohol, smoking, and physical activity.