Supplemental Material: Annu. Rev. Nutr. 2017. 37:293–320
https://doi.org/10.1146/annurev-nutr-071715-051004
Nature, Nurture, and Cancer Risks: Genetic and Nutritional Contributions to Cancer
Theodoratou et al.

Supplemental Table 1 General characteristics of the meta-analyses of prospective observational studies in breast cancer. Evidence class was decided on the basis of the following criteria: Convincing evidence (class I) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), a 95% prediction interval not including the null, no evidence of small-study effects, no evidence of excess significance bias, and not large heterogeneity ($I^2 < 50\%$). Highly suggestive evidence (class II) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), and the largest study to have a 95% CI that excluded 1. Suggestive evidence (class III) required only >1,000 cases and $P < 0.001$ by random effects. All other risk factors with nominally significant summary associations ($P < 0.05$) were coined as having weak evidence (class IV). Nonsignificant associations (NS) were those with $P > 0.05$.
(RR: relative risk, OR: odds ratio, HR: hazard ratios, CI: confidence interval, SRRE: summary relative risk estimates, NA: not applicable).

Risk factor	Reference	Population	Outcome	Unit of comparison	Participants	Events	No. of studies	Type of metric	Meta-analysis model	RR (95% CI)	*P* value	Prediction interval	I^2 (%)	Evidence class
Nutrient/dietary factor														
Alcoholic drinks[1]	Jung S, 2015	Female from North America, Japan, Europe, and Australia	Incidence of ER+ and ER- breast cancers	≥30 g/d of alcohol consumption vs nondrinkers	1,089,273	ER+: 21,232; ER-: 4,343	ER+: 20; ER-: 17	RR	Random	ER+: 1.35 (1.23--1.48); ER-: 1.28 (1.10--1.49)	ER+: 5.2×10^{-10}; ER-: 0.001	ER+: 1.07, 1.70	ER+: 26; ER-: 0	ER+: II[2]; ER-: IV
Marine *n*-3 polyunsaturated fatty acids	Zheng J-S, 2013	Female	Incidence	Highest vs lowest category	687,770	13,323	17	RR	Random	0.86 (0.78--0.94)	0.002	NA	54	IV
Egg	Si R, 2014	Female	Incidence of pre- and postmenopausal breast cancer	>1/week (>7 g/day) vs <1/week (<7 g/day)	722,908	15,173	11	RR	Random	1.04 (1.00--1.08)	0.05	NA	0	IV
Dairy	Dong J-Y, 2011	Female	Incidence	Highest vs lowest category	542,401	15,053	10	RR	Random	0.85 (0.76--0.95)	0.004	NA	54.5	IV
Polyunsaturated fat	Turner LB, 2011	Females	Incidence	Highest vs lowest quartile of dietary intake	1,051,623	20,405	13	RR	Random	1.09 (1.00--1.18)	0.04	NA	>50	IV
Processed meat	Alexander D, 2011	Females	Incidence	High vs low intake	NA	NA	18	SRRE	Random	1.08 (1.01--1.16)	0.03	NA	>50	IV

Soy	Dong J-Y, 2011	Female	Incidence	Highest vs lowest category	NA	5,587	14	RR	Random	0.89 (0.79--0.99)	0.04	NA	62.4	IV
Isoflavone	Xie Q, 2013	Females in Asian countries	Incidence	Highest vs lowest categories of isoflavone intake	129,103	NA	7	RR	NA	0.78 (0.65--0.95)	0.01	NA	NA	IV
Cruciferous vegetables	Liu X, 2013	USA females	Incidence	Highest vs lowest consumptions level	135,162	3,947	2	RR	Fixed	0.86 (0.72--0.99)	0.05	NA	3	IV
Vegetables	Jung S, 2012	Females	Incidence of ER- breast cancer	Highest vs lowest quintiles of total vegetables consumption	993,466	4,821	20	RR	Random	0.82 (0.74--0.90)	8.1×10^{-5}	NA	<50	III
Vegetables and fruits combined	Aune D, 2012	Females	Incidence	Highest vs lowest intake	233,036	6,273	6	RR	Random	0.89 (0.80--0.99)	0.03	NA	0	IV
Fruits	Aune D, 2012	Females	Incidence	Highest vs lowest intake	785,668	16,763	10	RR	Random	0.92 (0.86--0.98)	0.01	NA	9	IV
Retinol	Fulan H, 2011	Females	Incidence	Highest vs lowest intake of total retinol	NA	NA	8	RR	Fixed	0.91 (0.84--0.98)	0.02	NA	27	IV
Vitamin A	Fulan H, 2011	Females	Incidence	Highest vs lowest total intake	NA	NA	5	RR	Fixed	0.89 (0.81--0.99)	0.02	NA	0	IV
Glycemic index	Choi Y, 2012	Females from North America, Europe, and China	Incidence	Highest vs lowest category	NA	NA	11	RR	Random	1.06 (1.02--1.11)	0.007	NA	0	IV

α-carotene	**Hu F, 2012**	**Females**	**Incidence**	Per 1,500 lg/day of dietary intake	262,358	7,298	4	OR/RR	Random	**0.91 (0.87--0.96)**	**0.0002**	**NA**	1	III
β-carotene	Hu F, 2012	Females	Incidence	Highest vs lowest level of dietary intake	NA	NA	5	OR/RR	Random	0.94 (0.89--0.97)	0.005	NA	0	IV
Dietary fiber	Aune D, 2012	Females from Europe, North America, and Asia	Incidence	Highest vs lowest level of fiber intake	999,271	26,523	16	RR	Random	0.93 (0.89--0.98)	0.003	NA	0	IV
Biomarker														
n-3/*n*-6 PUFAs ratio in serum (plasma)	Yang B, 2014	Female, Europe, USA, Asia	Incidence of pre- and postmenopausal breast cancer	Highest category (tertile, quartile, and quintile) vs lowest or reference	274,135	8,331	11	RR	Random	0.90 (0.82--0.99)	0.03	NA	11	IV
Total carotenoids	Eliassen AH, 2012	Females	Incidence	Highest quintile to lowest quintile of blood level	3,941 (controls)	3,041	--	RR	Random	0.81 (0.68--0.96)	0.02	NA	<50	IV
β-carotene	Eliassen AH, 2012	Females	Incidence	Top vs bottom quintile of blood levels	3,953	3,053	8	RR	Random	0.83 (0.70--0.98)	0.03	NA	<50	IV
Lycopene	Eliassen AH, 2012	Females	Incidence	Top vs bottom quintile of blood levels	3,941	3,041	8	RR	Random	0.81 (0.68--0.96)	0.02	NA	<50	IV

[1] Current study was used instead of the bigger meta-analysis of 7 cohort studies on alcohol consumption and breast cancer risk by Bagnardi et al. 2015 (RR for heavy drinkers vs nondrinkers: 1.50; 95% CI: 1.19--1.89) due to the limited information on summary statistics and included studies in Bagnardi et al. 2015

[2] Evidence was classified as highly suggestive (class II) due to the presence of excess significance bias ($P_{\text{excess significance bias}} = 4 \times 10^{-8}$, $P_{\text{small effect bias}} = 0.184$)

Supplemental Table 2 General characteristics of the meta-analyses of prospective observational studies in lung cancer. Evidence class was decided on the basis of the following criteria: Convincing evidence (lass I) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), a 95% prediction interval not including 1, and not large heterogeneity ($I^2 < 50\%$). Highly suggestive evidence (class II) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), and the largest study to have a 95% CI that excluded 1. Suggestive evidence (class III) required only >1,000 cases and $P < 0.001$ by random effects. All other risk factors with nominally significant summary associations ($P < 0.05$) were coined as having weak evidence (class IV). Nonsignificant associations (NS) were those with $P > 0.05$. (RR: relative risk, OR: odds ratio, HR: hazard ratios, CI: confidence interval, SRRE: summary relative risk estimates, NA: not applicable).

Nutrient/Diet	Reference	Population	Outcome	Unit of comparison	Participants	Events	No. of studies	Type of metric	Meta-analysis model	RR (95% CI)	*P* value	Prediction interval	I^2 (%)	Evidence class
α-carotene	Gallicchio L, 2008	Western populations, Singapore	Incidence	Highest vs lowest category of intake	299,057	4,894	8	RR	Random	0.89 (0.79--1.00)	0.05	NA	15	IV
β-carotene	Yu N, 2015	Populations from North America, Europe, and China	Incidence	Highest vs lowest category	NA	5,395	10	RR	Random	0.87 (0.78--0.96)	0.009	NA	7	IV
β-cryptoxanthin	Gallicchio L, 2008	Western populations, Singapore	Incidence	Highest vs lowest category of intake	299,057	4,894	8	RR	Random	0.80 (0.72--0.89)	4.4×10^{-5}	NA	0	III
Lycopene	Gallicchio L, 2008	Western populations, Singapore	Incidence	Highest vs lowest category of intake	340,894	5,032	9	RR	Random	0.86 (0.77--0.97)	0.01	NA	20	IV
Lutein-zeaxanthin	Gallicchio L, 2008	Western populations, Singapore	Incidence	Highest vs lowest category of intake	169,334	3,945	5	RR	Random	0.89 (0.79--1.00)	0.05	NA	0	IV
Carotenoids	Gallicchio L, 2008	Western populations, Singapore	Incidence	Highest vs lowest category of intake	247,706	4,310	8	RR	Random	0.79 (0.71--0.87)	7.1×10^{-6}	NA	0	III

Vitamin A	Yu N, 2015	Populations from North America, Europe, and China	Incidence	Highest vs lowest category	NA	3,258	6	RR	Random	0.87 (0.76--0.98)	0.03	NA	53	IV
Soy food	Wu SH, 2013	--	Incidence	Highest vs lowest intake	NA	NA	4	RR	Fixed	0.85 (0.74--0.97)	0.02	NA	8	IV
Vegetables	Vieira AR, 2016	Populations from Asia, Europe, and North America	Incidence	Highest vs lowest intake	NA	19,095	25	RR	Random	0.92 (0.87--0.97)	0.002	NA	0	IV
Soy/soy isoflavones	Yang W-S, 2011	Females from Singapore and United States, and males and females from Japan	Incidence	Highest vs lowest intake	146,667	1,806	3	RR	Fixed	0.92 (0.85--0.98)	0.02	NA	0	IV
Cruciferous vegetables	Vieira AR, 2016	Populations from Asia, Europe, and North America	Incidence	Dose response per 50 g/day	NA	5,783	9	RR	Random	0.89 (0.79--1.00)	0.05	NA	50	IV
Total fruits and vegetables	Vieira AR, 2016	Populations from Asia, Europe, and North America	Incidence	Highest vs lowest intake	NA	11,941	18	RR	Random	0.86 (0.78--0.94)	0.002	NA	37	IV
Fruits	Vieira AR, 2016	Populations from Asia, Europe, and North America	Incidence	Highest vs lowest intake	NA	15,599	29	RR	Random	0.82 (0.76--0.89)	1×10^{-6}	0.62, 1.07	32	II

Citrus fruits	Vieira AR, 2016	Populations from Asia, Europe, and North America	Incidence	Highest vs lowest intake	NA	12,021	15	RR	Random	0.85 (0.78--0.93)	0.0003	NA	30	III
Flavonoids	Tang N-P, 2009	Western populations	Incidence	Highest vs non/lowest intake	235,816	3,247	8	RR	Random	0.73 (0.57--0.93)	0.01	NA	69	IV

Supplemental Table 3 General characteristics of the meta-analyses of prospective observational studies in prostate cancer. Evidence class was decided on the basis of the following criteria: Convincing evidence (class I) required >1,000 cases, highly significant summary associations (*P* < 10^{-6} by random effects), a 95% prediction interval not including the null, and not large heterogeneity (I^2 < 50%). Highly suggestive evidence (class II) required >1,000 cases, highly significant summary associations (*P* < 10^{-6} by random effects), and the largest study to have a 95% CI that excluded 1. Suggestive evidence (class III) required only >1,000 cases and *P* < 0.001 by random effects. All other risk factors with nominally significant summary associations (*P* < 0.05) were coined as having weak evidence (class IV). Nonsignificant associations (NS) were those with *P* > 0.05. (RR: relative risk, OR: odds ratio, HR: hazard ratios, CI: confidence interval, SRRE: summary relative risk estimates, NA: not applicable).

Risk factor	Reference	Population	Outcome	Unit of comparison	Participants	Events	No. of studies	Type of metric	Meta-analysis model	RR (95% CI)	*P* value	Prediction interval	I^2 (%)	Evidence class
Nutrient/dietary factor														
Alpha - linolenic acid (*n*-3 PUFA)	Fu Y-Q, 2014	Men from Western countries	Incidence	Per 0.5 g/day	NA	NA	5	RR	Random	0.99 (0.98--1.00)	0.05	NA	0	IV
Total dairy	Aune D, 2015	Men	Incidence	Highest vs lowest intake	848,395	38,107	15	RR	Random	1.09 (1.02--1.17)	0.01	NA	43	IV
Milk	Aune D, 2015	Men	Incidence	High vs low intake	566,146	11,392	15	RR	Random	1.11 (1.03--1.21)	0.01	NA	21	IV
Whole milk	Aune D, 2015	Men	Incidence	High vs low intake	448,719	19,664	8	RR	Random	0.92 (0.85--0.99)	0.03	NA	0	IV
Low-fat milk	Aune D, 2015	Men	Incidence	High vs low intake	432,943	19,430	6	RR	Random	1.14 (1.05--1.25)	0.003	NA	51	IV
Cheese	Aune D, 2015	Men	Incidence	High vs low intake	887,759	22,950	11	RR	Random	1.07 (1.01--1.13)	0.02	NA	0	IV
Dietary Calcium	Aune D, 2015	Men	Incidence	High vs low intake	800,879	35,493	15	RR	Random	1.18 (1.08--1.30)	0.0005	NA	53	III
Eggs	Keum N, 2015	Men from Europe, North America, and Japan	Incidence of fatal prostate cancer	Per 5 eggs consumed/week	95,980	609	4	RR	Random	1.47 (1.01--2.14)	0.04	NA	40	IV
Selenium	Vinceti M, 2014	Men	Incidence	Highest vs lowest category of intake and biochemical selenium level	>466,204	6,532	17	OR/RR	Random	0.79 (0.69--0.90)	0.0005	NA	23	III

Biomarkers														
Stearic acid (saturated fatty acid)	Crowe FL, 2014	Men from Western countries	Incidence	Fifth quantile vs first quantile of level in plasma or serum phospholipids, whole blood, or erythrocyte membranes	11,747	5,098	7	OR	NOT CLEAR	0.88 (0.78--1.00)	0.04	NA	10	IV
Eicosapentaenoic acid (*n*-3 PUFA)	Crowe FL, 2014	Men from Western countries	Incidence	Fifth quantile vs first quantile of level in plasma or serum phospholipids, whole blood, or erythrocyte membranes	11,745	5,098	7	OR	NOT CLEAR	1.14 (1.01--1.29)	0.04	NA	59	IV
Docosapentaenoic acid (*n*-3 PUFA)	Crowe FL, 2014	Men from Western countries	Incidence	Fifth quantile vs first quantile of level in plasma or serum phospholipids, whole blood, or erythrocyte membranes	11,744	5,097	7	OR	NOT CLEAR	1.16 (1.02--1.33)	0.03	NA	80	IV
Linoleic acid (*n*-6 PUFA)	Crowe FL, 2014	Men from Western countries	Incidence	Fifth quantile vs first quantile of level in plasma or serum phospholipids, whole blood, or erythrocyte membranes	11,747	5,098	7	OR	NOT CLEAR	0.87 (0.77--0.98)	0.02	NA	0	IV
Folate	TIo M, 2014	Men	Incidence	High vs low blood concentration	9,778	5,904	6	OR	Random	1.14 (1.02--1.28)	0.02	NA	0	IV

Supplemental Table 4 General characteristics of the meta-analyses of prospective observational studies in colorectal cancer. Evidence class was decided on the basis of the following criteria: Convincing evidence (class I) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), a 95% prediction interval not including 1, no evidence of small-study effects, no evidence of excess significance bias, and no large heterogeneity ($I^2 < 50\%$). Highly suggestive evidence (class II) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), and the largest study to have a 95% CI that excluded 1. Suggestive evidence (class III) required only >1,000 cases and $P < 0.001$ by random effects. All other risk factors with nominally significant summary associations ($P < 0.05$) were coined as having weak evidence (class IV). Nonsignificant associations (NS) were those with $P > 0.05$.

(RR: relative risk, OR: odds ratio, HR: hazard ratios, CI: confidence interval, SRRE: summary relative risk estimates, NA: not applicable).

Risk factor	Reference	Population	Outcome	Unit of comparison	Participants	Events	No. of studies	Type of metric	Meta-analysis model	RR (95% CI)	*P* value	Prediction interval	I^2 (%)	Evidence class
Nutrient/dietary factor														
Multivitamins supplements	Heine-Bröring RC, 2015	Western populations, USA, Europe	Incidence of CRC	Use vs no use	1,031,046	9,925	16	RR	Random	0.92 (0.86--0.98)	0.01	NA	0	IV
Vitamin A supplements	Heine-Bröring RC, 2015	Western populations, USA, Europe	Incidence of colon cancer	Use vs no use	46,796	443	2	RR	Random	0.77 (0.62--0.94)	0.01	NA	0	IV
Total vitamin C	Park Y, 2010	North America, Europe	Incidence and mortality of colon cancer	Highest vs lowest category (>600 vs <100 mg/day)	556,510	4,495	10	RR	Random	0.86 (0.74--0.99)	0.04	NA	<50	IV
Total vitamin E	Park Y, 2010	North America, Europe	Incidence and mortality of colon cancer	Highest vs lowest category (>200 vs ≤6 mg/day)	556,510	4,495	10	RR	Random	0.80 (0.65--0.97)	0.05	NA	<50	IV
Calcium	Keum N, 2014	USA, Europe, Asia	Incidence of colorectal and colon cancers	300 mg daily increment of calcium intake	1,415,597	12,305	15	RR	Random	0.92 (0.89--0.94)	4.8×10^{-9}	0.85, 1.01	47	II
Calcium supplements	Heine-Bröring RC, 2015	Western populations, USA, Europe	Incidence of CRC	Use vs no use	1,185,310	10,188	8	RR	Random	0.86 (0.79--0.95)	0.001	NA	64	IV

Folic acid supplements	Heine-Bröring RC, 2015	Western populations, USA, Europe	Incidence of CRC	Highest vs lowest dietary supplementation dose	291,006	4,057	3	RR	Random	0.88 (0.78--0.98)	0.03	--	6	IV
Total folate	Kim D-H, 2010	North America, Europe	Incidence and mortality of CRC	Highest vs lowest quantile	725,134	5,720	13	RR	Random	0.85 (0.77--0.95)	0.002	NA	<50	IV
Heme iron	Qiao L, 2013	North America, Europe, Japan	Incidence of CRC	Highest vs lowest category of intake	651,272	8,269	8	RR	Random	1.14 (1.04--1.25)	0.005	NA	12	IV
Zink	Qiao L, 2013	North America, Europe, Japan	Incidence of CRC	Highest vs lowest category of intake	350,507	5,676	6	RR	Random	0.83 (0.72--0.94)	0.006	NA	35	IV
Magnesium	Ko HJ, 2014	Europe, Japan, USA	Incidence of CRC	Highest vs lowest category of dietary intake	222,091	3,305	4	RR	Fixed	0.78 (0.66--0.92)	0.003	NA	17	IV
Total fiber	Aune D, 2011	Europe, China, Japan, Singapore, USA	Incidence of CRC	High vs low intake	1,995,293	14,794	19	RR	Random	0.88 (0.82--0.94)	0.0003	NA	0	III
Glycemic index (GI)	Choi Y, 2012	North America, Europe, China	Incidence of CRC	Highest vs lowest category	1,110,891	12,573	9	RR	Random	1.08 (1.00--1.17)	0.05	NA	29	IV
Alcohol[1]	Fedirko V, 2011	North America, Europe, Asia	Incidence of CRC	Heavy drinkers (≥50 g/day) vs nondrinkers/occasional drinkers	988,878	1,208	7	RR	Random	1.57 (1.38--1.80)	4.2×10^{-11}	1.32, 1,87	0	I[2]

Tea	Zhang X, 2010	North America, Europe	Incidence of colon cancer	Highest intake vs nonconsumers	604,710	4,394	11	RR	Random	1.28 (1.02--1.61)	0.03	NA	NA	IV
Fruit and vegetables combined	Aune D, 2011	Japan, Europe, USA, Singapore	Incidence of CRC	Highest vs lowest intake	1,523,860	11,853	10	RR	Random	0.92 (0.86--0.99)	0.02	0.85, 0.99	22	IV
Fruits	Aune D, 2011	Japan, Europe, USA	Incidence of CRC	Highest vs lowest intake	1,558,147	14,876	14	RR	Random	0.90 (0.83--0.98)	0.01	0.85, 0.96	42	IV
Vegetables	Aune D, 2011	Japan, Europe, USA, Singapore	Incidence of CRC	Highest vs lowest intake	1,694,236	16,057	15	RR	Random	0.91 (0.86--0.96)	0.0008	0.86, 0.96	0	III
Whole grains	Aune D, 2011	Europe, USA	Incidence of CRC	High vs low intake	642,060	5,477	4	RR	Random	0.79 (0.72--0.86)	3.1×10^{-7}	0.65, 0.96	0	I [3]
Fish	Yu XF, 2014	Europe, USA, Asia, Australia	Incidence of CRC	Yes vs no intake	1,633,066	14,097	20	RR	Random	0.93 (0.87--0.99)	0.03	NA	65	IV
Dairy products	Aune D, 2012	Europe, USA, Asia	Incidence of CRC	Highest vs lowest dietary intake	1,170,942	11,579	12	RR	Random	0.81 (0.74--0.90)	2.9×10^{-5}	NA	42	III
Nonfermented milk	Ralston RA, 2014	Europe, USA, China	Incidence of CRC and of colon and rectal cancers	Highest vs lowest category	892,569	7,735	14	RR	Random	0.85 (0.77--0.93)	0.0008	NA	0	III
Milk	Aune D, 2012	Europe, USA, China	Incidence and mortality of CRC	Per 200 g/day intake	566,035	4,510	9	RR	Random	0.91 (0.85--0.94)	0.0003	NA	0	III
Red meat	Alexander DD, 2011	Europe, USA, Canada, Australia, Asia	Incidence and mortality of CRC	Highest vs lowest intake	1,892,868	16,560	25	RR	Random	1.12 (1.04--1.21)	0.003	NA	>50	IV

Processed meat	Chan DSM, 2011	Europe, USA, Australia	Incidence and mortality of CRC	Per 50 g/day	1,303,149	10,863	9	--	--	1.18 (1.10--1.28)	2.3×10^{-5}	NA	12	III
Beef	Carr P, 2015	Europe, Japan	Incidence of CRC and of colon and rectal cancers	Highest versus lowest level of intake	CRC: 657,469 Colon: 179,429	CRC: 4,545 Colon: 2,160	CRC: 5; Colon: 3	RR	Random	Colorectal: 1.11 (1.01--1.22) Colon: 1.24 (1.07--1.44)	CRC: 0.03 Colon: 0.005	NA	CRC: 0 Colon: 11	IV
Lamb	Carr P, 2015	Europe	Incidence of CRC and of colon and rectal cancers	Highest versus lowest level of intake	532,028	CRC: 1,329 Colon: 644 Rectal: 345	CRC: 2	RR	Random	CRC: 1.24 (1.08--1.44)	0.003	NA	CRC: 0	IV
Poultry	Carr P, 2015	Europe, Asia, North America	Incidence of CRC and of colon and rectal cancers	Highest versus lowest level of intake	1,422,299	81,211	Rectal: 11	RR	Random	Rectal: 0.89 (0.80--0.98)	Rectal: 0.02	NA	Rectal: 0	IV
Biomarkers														
Circulating Vitamin D (25(OH)D)	Lee JE, 2011	USA, Japan, Europe	Incidence of colon cancer and rectal cancer	Top versus bottom quantiles of circulating 25(OH)D levels	NA	1,822 colon cancer and 868 rectal cancer cases	8	OR	Random	0.66 (0.54--0.81)	6.8×10^{-5}	NA	NA	III
Total *n*-3 PUFA - sum of C22:6*n*-3, C22:5*n*-3, C20:5*n*-3 compositions in human biospecimens	Yang B, 2014	Europe, USA, Japan	Incidence of colorectal cancer	Highest vs lowest levels in serum, plasma, whole blood, erythrocytes, adipose tissue	58,713	675	3	RR	Random	0.76 (0.59--0.97)	0.03	NA	10	IV

[1]Current study was used instead of the bigger meta-analysis of 14 cohort studies on alcohol consumption and colorectal cancer risk by Bagnardi et al. 2015 (RR for heavy drinkers vs non-drinkers: 1.41; 95% CI, 1.23--1.63) due to the limited information on summary statistics and included studies in Bagnardi et al. 2015

[2]No evidence of small effect ($P_{\text{small effect bias}} = 0.802$) or excess significance bias ($P_{\text{excess significance bias}} = 0.254$)

[3]No evidence of small effect ($P_{\text{small effect bias}} = 0.947$) or excess significance bias ($P_{\text{excess significance bias}} = 0.11$)

Supplemental Table 5 General characteristics of the meta-analyses of prospective observational studies in stomach cancer. Evidence class was decided on the basis of the following criteria: Convincing evidence (class I) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), a 95% prediction interval not including the null, and not large heterogeneity ($I^2 < 50\%$). Highly suggestive evidence (class II) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random-effects), and the largest study to have a 95% CI excluding the null value. Suggestive evidence (class III) required only >1,000 cases and $P < 0.001$ by random effects. All other risk factors with nominally significant summary associations ($P < 0.05$) were coined as having weak evidence (class IV). Nonsignificant associations (NS) were those with $P > 0.05$.
(RR: relative risk, OR: odds ratio, HR: hazard ratios, CI: confidence interval, SRRE: summary relative risk estimates, NA: not applicable).

Nutrient/dietary intake	Reference	Population	Outcome	Unit of comparison	Participants	Events	No. of studies	Type of metric	Meta-analysis model	RR (95% CI)	*P* value	Prediction interval	I^2 (%)	Evidence class
Vitamin E	Li P, 2014	USA, Europe	Incidence	Highest vs lowest intake	557,765	1,198	4	RR	Fixed	0.81 (0.66--0.98)	0.04	NA	0	IV
Vitamin C	Li P, 2014	Europe, USA	Incidence	Highest vs lowest intake	66,095	795	4	HR/RR	Fixed	0.77 (0.61--0.97)	0.03	NA	0	IV
High-salt food	Fang X, 2015	Asia, Europe	Incidence/mortality	Highest vs lowest intake	274,250	2,271	12	RR	Random	1.55 (1.17--2.05)	0.002	NA	53	IV
Salt	Fang X, 2015	Asia, Europe	Incidence/mortality	Highest vs lowest intake	2,569,145	14,850	8	RR	Random	1.11 (1.05--1.16)	4.7×10^{-5}	NA	26	III
Alcohol	Fang X, 2015	Asia, Europe, USA	Incidence/mortality	Highest vs lowest intake	2,511,522	9,469	24	RR	Random	1.15 (1.01--1.31)	0.03	NA	64	IV
Beer	Fang X, 2015	Asia, Europe, USA	Incidence/mortality	Highest vs lowest intake	1,197,197	2,482	13	RR	Random	1.21 (1.02--1.43)	0.03	NA	31	IV
Liquor	Fang X, 2015	Asia, Europe, USA	Incidence/mortality	Highest vs lowest intake	1,197,197	2,482	12	RR	Random	1.22 (1.05--1.43)	0.01	NA	6	IV
Total fruits	Fang X, 2015	Asia, Europe, USA	Incidence/mortality	Highest vs lowest intake	2,811,612	7,632	30	RR	Random	0.93 (0.89--0.98)	0.003	NA	2	IV
Fruits	Wang Q, 2014	USA, Europe, Asia	Incidence/mortality	High vs low intake	1,517,969	5,318	22	SRR	Random	0.90 (0.83--0.98)	0.01	NA	1%	IV
Citrus fruit	Fang X, 2015	Asia, Europe, USA	Incidence/mortality	Highest vs lowest intake	2,846,394	4,259	11	RR	Random	0.90 (0.82--1.00)	0.04	NA	41	IV
White vegetables	Fang X, 2015	Japan	Incidence/mortality	Highest vs lowest intake	51,186	531	6	RR	Random	0.67 (0.47--0.95)	0.03	NA	0	IV
Pickled vegetables	Fang X, 2015	Asia, Europe	Incidence/mortality	Highest vs lowest intake	540,913	6,840	20	RR	Random	1.18 (1.02--1.36)	0.02	NA	55	IV
Tomatoes	Fang X, 2015	Asia, Europe, USA	Incidence/mortality	Highest vs lowest intake	722,446	1,869	5	RR	Random	1.11 (1.01--1.22)	0.03	NA	0	IV

Nutrient/dietary intake	Reference	Population	Outcome	Unit of comparison	Participants	Events	No. of studies	Type of metric	Meta-analysis model	RR (95% CI)	*P* value	Prediction interval	I^2 (%)	Evidence class
Spinach	Fang X, 2015	Asia, Europe, USA	Incidence/mortality	Highest vs lowest intake	722,446	1,869	5	RR	Random	1.21 (1.01--1.46)	0.04	NA	0	IV
Pickled food	Ren J-S, 2012	Asia, USA, Europe	Incidence/mortality	Picked vegetables/food users vs non-users or lowest category of use	224,879	3,692	10	RR	Random	1.32 (1.10--1.59)	0.003	NA	70	IV
Salted fish	Fang X, 2015	Asia, Europe, USA	Incidence/mortality	Highest vs lowest intake	291,071	2,811	11	RR	Random	1.25 (1.07--1.47)	0.006	NA	0	IV
Processed meat	Fang X, 2015	Asia, Europe, USA	Incidence/ mortality	Highest vs lowest intake	2,002,100	3,243	13	RR	Random	1.15 (1.03--1.29)	0.01	NA	8	IV
Ham, bacon, sausage	Fang X, 2015	Asia, Europe, USA	Incidence/mortality	Highest vs lowest intake	321,858	1,573	11	RR	Random	1.21 (1.01--1.46)	0.04	NA	31	IV

Supplemental Table 6 General characteristics of meta-analyses of RCTs.[a] Evidence class was decided on the basis of the following criteria: Convincing evidence (class I) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), a 95% prediction interval not including the null, and not large heterogeneity ($I^2 < 50\%$). Highly suggestive evidence (class II) required >1,000 cases, highly significant summary associations ($P < 10^{-6}$ by random effects), and the largest study to have a 95% CI that excluded 1. Suggestive evidence (class III) required only >1,000 cases and $P < 0.001$ by random effects. All other risk factors with nominally significant summary associations ($P < 0.05$) were coined as having weak evidence (class IV). Nonsignificant associations (NS) were those with $P > 0.05$.
(RR: relative risk, OR: odds ratio, HR: hazard ratios, CI: confidence interval, SRRE: summary relative risk estimates, NA: not applicable).

Nutrients/food	Author	Date	Control population	Population	Participants total	Events total	Type of metric	Meta-analysis model	No. of studeis	Reported RR (95% CI)	Heterogeneity, I^2(%), $P_{heterogeneity}$	*P* value	Class	Notes
BREAST CANCER														
LUNG CANCER														
β-carotene	Tanvetyanon T	2008		High-risk populations (smokers, exposed to asbestos)	109,394	1,484	OR	Random	4	1.21 (1.09--1.32)	32.5%, 0.22	0.000108	III	Effect stronger in current smokers (OR: 1.24, 95% CI: 1.10--1.39), no effect in former smokers and never smokers
PROSTATE CANCER														
Folic acid	Vollset S.E.	2013	Placebo	Patient with previous colorectal adenoma, people with or at high risk of the cardiovascular disease	49,621	656	RR	Random	13	1.15 (0.94--1.41)	NA		NS	

Calcium supplementations	Bristow S.M.	2013	Placebo	General populations or patients with osteoporosis or colorectal adenoma	7,221	24	HR	Random	4	0.54 (0.30--0.96)	0%	0.04	IV	
Soy/isoflavones	Diana van Die M	2013	Placebo or soy protein isolate with isoflavones removed	Males with clinically identified risk (negative prostate biopsy)	122	32	RR	Fixed	2	0.49 (0.26--0.95)	42%, 0.19	0.03	IV	
BOWEL CANCER														
STOMACH CANCER														

[a]No meta-analyses on randomized clinical studies for corresponding cancer types were identified.

Supplemental Table 7 General characteristics of meta-analyses for gene--environment interactions (RR: relative risk, OR: odds ratios, CI: confidence interval)[a]

Nutrient /food	Genetic variant	Gene (or near gene)	Author, date	Participants	Events	Type of metric	Meta-analysis model	No. of studies	Reported RR (95% CI)	*P* for inter	Heterog, P_h	Prior score category (based on dietary factors and genetic variants evidence)	Venice Criteria for observed association	Combined score
BREAST CANCER														
Alcohol	rs4880	*MnSOD*	Liu G, 2012	3,064	1,301	OR	Non drinkers Fixed Ever drinkers Random	14	Val/Ala+Ala/ALA vs Val/Val Nondrinkers: 0.97 (0.80--1.18) Ever drinkers: 1.42 (0.89--2.26)	>0.05	Nondrinkers: 0.31 Ever drinkers: 0.02	Weak: 3	CCC	No evidence
	rs17468277	*CASP8*	Nickels S, 2013	15,386	6,081	OR	Fixed	24	<20 g/day alcohol: 0.91 (0.84--0.98) ≥20 g/day 1.45 (1.14--1.85)	0.0003	0.30	Weak: 3	CBC	Weak evidence
	rs1045485	*CASP8*	Barrdahl M, 2014	40,376	17,988	OR	Random	2 consortia	1.14 (0.98--1.31)	0.08	0.006	Weak: 3	CCC	No evidence

	rs2853826 (A10398G)	*ND3*	Blein S, 2014	3,983 (controls)	3306	OR		Breast and Prostate Cancer Cohort Consortium (9 cohorts)	Breast cancer risk G10398 – Drinkers vs. A10398 - Nondrinkers 1.16 (0.99-- 1.36)	0.98		Weak: 3	C-C	No evidence
	rs698	*ADH1C*	Mao Q, 2015	3,434	1610	OR		3	ADH1C [1-1] + ADH1C [1-2] in drinkers: 1.35 (1.03--1.76) ADH1C [1-1] + ADH1C [1-2] in nondrinkers: 1.16 (0.86--1.57)	NR	Drinkers P = 0.89 Nondrinkers P = 0.53	Weak: 3	--C	Not possible to evaluate
Carotenoids	rs2333227 (G463A)	*MPO*	Pabalan N, 2012	4,915	2,192	OR	Fixed	2	A vs G For low carotenoid intake: 1.05 (0.92--1.20) For high carotenoid intake: 0.86 (0.75--0.99)	0.88	0.14	Weak: 3	BBC	No evidence
LUNG CANCER														

PROSTATE CANCER														
COLORECTAL CANCER														
Alcohol	rs1805087 (A2756G)	*MTR*	Ding W, 2013	3,934	1,398	OR	Random	4	Heavy alcohol drinkers (≥50 g ethanol/d on ≥5 day/week) with the G allele vs. the wild AA genotype: 2.00 (1.28--3.09)	0.002	0.38	Weak: 3	-BB	Weak evidence
	rs1042522 (Pro72Arg)	*p53*	Liu Y, 2011	1,464	501	OR		2 Asian studies	Alcohol consumers vs. nonconsumers Arg/Arg: 0.67 (0.41--1.09) Pro/Pro: 0.91 (0.52--1.57)	Arg/Arg 0.11 Pro/Pro 0.73		Weak: 3	--C	No evidence
Vegetables	rs16892766	8q23.3	Hutter CM, 2012	16,739	7,016	OR	Fixed	9 GWAS	1.88 (1.36--2.59)	0.02	0.68	Moderate: 2	CBB	Weak Evidence

Cruciferous vegetables	Present/null	*GSTM1* and *GSTT1*	Tse G, 2014	11,144	3,556	OR		6	Double null 0.86 (0.70--1.06) Double non-null 1.11 (0.86--1.43)	NS	-	Weak: 3	-CB	No evidence
	Present/null	*GSTM1*	Tse G, 2014	12,383	4,016	OR		8	Single null: 1.05 (0.92--1.19) Single non-null: 1.02 (0.92--1.13)	NS	-	Weak: 3	-CB	No evidence
	Present/null	*GSTT1*	Tse G, 2014	11,144	3,556	OR		6	Single null: 0.78 (0.64--0.95) Single non-null: 1.02 (0.90,--1.13)	<0.05	-	Weak: 3	-CB	Weak evidence
Processed meat	rs4143094	10p14	Figueiredo JC, 2014	18,404	9,287	OR	Fixed	10 GWAS	1.17 (1.11--1.23)	8.7E-09	0.78	Weak: 3	BBB	Moderate evidence

[a]No meta-analyses on gene—diet interactions were identified for corresponding cancer types and foods and nutrients for which the evidence was classified as I, II, or III.

Supplemental Table 8 Evaluation of genetic evidence for variants identified in gene-environment interaction literature search. Evidence class was decided on the basis of the HuGENet Venice criteria (9, 10): Only genetic effects with $P < 10^5$ were considered for evaluation. On the basis of a combination of three criteria (amount of evidence, degree of replication, and protection from bias) (each of which can be scored A, B, or C), the epidemiological evidence for an effect of the genotype is classified as strong, moderate, or weak. For amount of evidence, a grade of A, B, or C was assigned when the sample size for the rarer genotype in the meta-analyses was greater than 1,000, 100--1,000, or less than 100, respectively. For replication consistency, we used I^2 <25% to assign grade A, 25--50% to assign grade B, and >50% or a *P* value for heterogeneity <0.10 to assign grade C. For protection from bias, a grade of A means that bias, if present, may change the magnitude but not the presence of an association; a grade of B means that there is no evidence of bias that would invalidate an association, but important information is missing; and a grade of C means that there is a strong possibility of bias that would render the finding of an association invalid.

Traits	Genetic variant	Gene (or near gene)	Author, date	Discovery sample size	Replication sample size/no. of studies in meta-analysis	Type of metric	EAF	Reported RR (95% CI)	*P*	Heterog, P_h	Venice criteria	Evidence class
Breast cancer	rs4880, Val16Ala	*mnSOD*	Qiu L-X, 2010	26,022 cases and 32,426 controls	NA, meta-analysis of 32 studies	OR	Not available	Val/Ala vs. Val/Val: OR = 1.022, 95% CI = 0.981–1.064; Ala/Ala vs. Val/Val: OR = 1.006, 95% CI = 0.934–1.083; dominant model: OR = 1.013, 95% CI = 0.962–1.066; and recessive model: OR = 0.985, 95% CI = 0.931–1.042	Val/Ala vs. Val/Val: *P* = 0.2976; Ala/Ala vs. Val/Val: *P* = 0.8833; dominant model: *P* = 0.6345; and recessive model: *P* = 0.6113	Val/Ala vs. Val/Val: P_h = 0.103; Ala/Ala vs. Val/Val: P_h = 0.004; dominant model: P_h = 0.028; and recessive model: P_h = 0.023	-	NS
	rs17468277/rs1045485 (D302H)*	*CASP8*	Lin W-Y, 2015	46,450 cases and 42,600 controls of European ancestry	10,052 cases and 12,575 controls of European ancestry	OR	0.11	0.94 (0.875--1.01)	0.0947	I^2 = 79%, P_h = 0.0288	-	NS

	rs2853826 (A10398G)	*ND3*	Blein S, 2014	13,511 cases with postmenopausal breast cancer and matched controls	Meta, 5 studies	OR	Not provided	Results not provided	Results not provided	Results not provided	-	NS
	rs698	*ADH1C*	Wang L, 2012	6,159 cases and 5,732 controls of European ancestry	Meta, 12 studies	OR	Not provided	1.01 (0.97--1.06)	0.67	P_h = 0.574	-	NS
	rs2333227 (G463A)	*MPO*	Pabalan N, 2012	2,975 cases and 3,427 controls	Meta, 3 studies	OR	0.20-0.26	Per allele effect: premenopausal: 0.88 (0.72--1.06); postmenopausal cancer: 1.01 (0.95--1.12)	Per allele effect: premenopausal: 0.19; postmenopausal cancer: 0.77	Per allele effect: premenopausal: I^2 = 5%, P_h = 0.31; postmenopausal cancer: I^2 = 0%, P_h = 0.54	-	NS
Colorectal cancer	rs1805087 (A2756G)	*MTR*	Zhao Y, 2013	13,465 patients and 20,430 controls	Meta, 26 studies	OR	0.06-0.25	1.03 (0.96--1.09)	0.25	P_h = 0.008	-	NS
	rs1042522 (A2756G)	*P53*	Ma X, 2014	10,515 cases and 12,909 controls	Meta, 31 studies	OR	0.3128	1.00 (0.92--1.10)	0.922	I^2 = 72%, P_h < 0.01	-	NS
	rs16892766	8q23.3, *EIF3H*	Li M, 2015	41,728 cases and 44,393 controls	Meta, 11 studies	OR	0.1	1.22 (1.18--1.27)	1.39×10^{-24}	I^2 = 4%, P = 0.39	AAA	Strong

	Deletion	*GSTM1*	Ma X, 2014	20,552 cases and 31,419 controls	Meta, 56 studies	OR	0.5	1.1 (1.04--1.17)	0.001	I^2 = 48%, P < 0.01	-	NS
	Deletion	*GSTT1*	Qin X-P et al., 2013	15,373 colorectal cancer cases and 21,238 controls	Meta, 46 studies	OR	NA	1.21 (1.10--1.33)	9.5×10^{-5}	I^2 = 67.4%, P < 0.001	-	NS
	rs4143094	10p14	Figueiredo JC, 2014	9,287 cases and 9,117 controls	Meta, 10 studies	OR	NA	NA	0.26	NA	-	NS

NS: non significant, where significance is defined as $P < 10^{-5}$; OR: odds ratios; P_h: P value for Cochran's Q statistic test; EAF: effect allele frequency; NA: not available; -: not applicable

*rs17468277 and rs1045485 variants are in linkage disequilibrium and have r2 = 1 and D' = 1 in European populations. Both variants are often used interchangeably in genetic association studies and meta-analyses.