Supplemental Table S1: Correlations and associations of early detection markers with lifestyle factors among controls (*N*=217) [a]

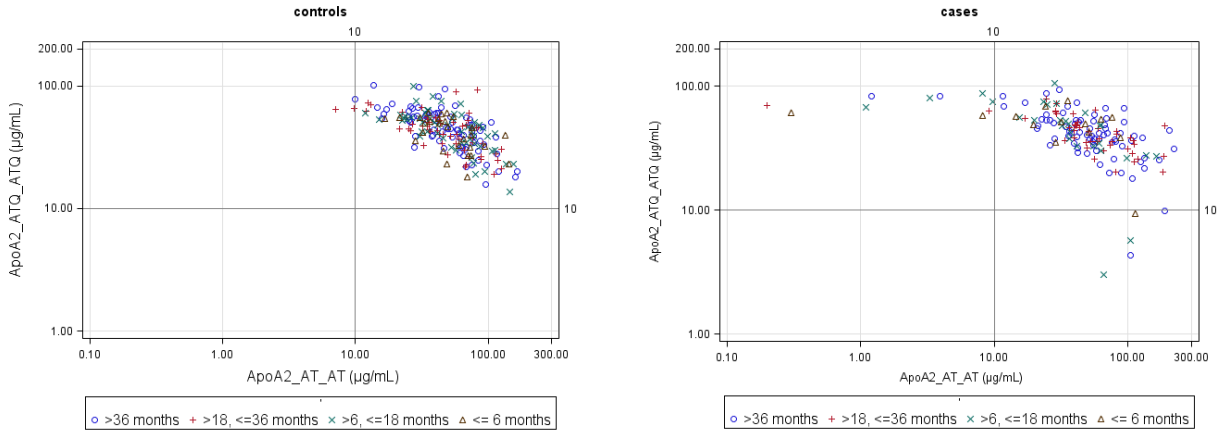
	CA19-9	ApoA2-ATQ/AT	ApoA2-AT/AT	ApoA2-ATQ/ATQ
CA19-9		r = -0.04 *P* = 0.547	r = -0.08 *P* = 0.239	r = 0.05 *P* = 0.509
ApoA2-ATQ/AT			**r = 0.65** ***P* < 0.0001**	r = 0.07 *P* = 0.279
ApoA2-AT/AT				**r = -0.60** ***P* < 0.0001**
HbA1c[b]	r = 0.11 *P* = 0.262	r = 0.08 *P* = 0.439	r = -0.03 *P* = 0.757	r = 0.09 *P* = 0.361
Age at baseline	r = 0.12 *P* = 0.086	**r = -0.13** ***P* = 0.048**	r = -0.04 *P* = 0.538	r = -0.04 *P* = 0.517
Sex				
Women (n=102)	0.91 (0.72-1.15)	**1.36 (1.04-1.79)**	**1.21 (1.10-1.33)**	0.82 (0.69-0.97)
BMI	r = -0.08 *P* = 0.273	r = -0.08 *P* = 0.262	r = -0.07 *P* = 0.289	r = 0.06 *P* = 0.381
<25 kg/m² (n=88)	Ref	Ref	Ref	Ref
≥25 kg/m² (129)	0.87 (0.69-1.08)	1.16 (0.87-1.54)	1.00 (0.91-1.10)	1.14 (0.95-1.37)
Alcohol, baseline	**r = 0.15** ***P* = 0.033**	**r = 0.19** ***P* = 0.007**	r = 0.06 *P* = 0.417	**r = 0.15** ***P* = 0.032**
None (n=25)	Ref	Ref	Ref	Ref
>0-12g/d (n=101)	0.89 (0.59-1.35)	1.41 (0.89-2.24)	1.11 (0.94-1.30)	0.95 (0.73-1.24)
>12-24g/d (n=36)	0.74 (0.41-1.34)	**2.05 (1.17-3.58)**	1.19 (0.99-1.45)	0.90 (0.64-1.25)
>24-60g/d (n=43)	0.82 (0.48-1.41)	**2.63 (1.50-4.62)**	**1.34 (1.11-1.62)**	0.87 (0.62-1.21)
≥60g/d (n=11)	1.20 (0.76-1.87)	**2.73 (1.18-6.32)**	0.92 (0.63-1.34)	**1.66 (1.07-2.60)**
	P het = 0.512	***P* het = 0.005**	***P* het = 0.010**	***P* het = 0.041**
Alcohol, lifetime	r = 0.08 *P* = 0.268	**r = 0.16** ***P* = 0.021**	r = 0.09 *P* = 0.193	r = 0.01 *P* = 0.934
None, ex (n=23)	Ref	Ref	Ref	Ref
>0-12g/d (n=100)	0.78 (0.51-1.19)	1.56 (0.54-2.54)	1.18 (0.99-1.41)	0.89 (0.69-1.16)
>12-24g/d (n=35)	0.84 (0.49-1.43)	**2.67 (1.48-4.83)**	**1.32 (1.07-1.61)**	0.93 (0.67-1.29)
>24-60g/d (n=31)	1.10 (0.74-1.63)	**2.42 (1.27-4.61)**	**1.28 (1.02-1.60)**	0.92 (0.65-1.31)
≥60g/d (n=13)	0.96 (0.54-1.59)	2.32 (1.00-5.40)	1.27 (0.94-1.71)	0.99 (0.65-1.50)
	P het = 0.519	***P* het = 0.012**	*P* het = 0.116	*P* het = 0.924
Diabetes [c]				
no (n=181)	Ref	Ref	Ref	Ref
yes (n=16)	1.17 (0.91-1.51)	0.96 (0.53-1.71)	0.96 (0.77-1.19)	1.06 (0.78-1.44)
Smoking				
never (n=95)	Ref	Ref	Ref	Ref
former (n=79)	1.20 (0.87-1.65)	0.80 (0.58-1.12)	**0.85 (0.75-0.95)**	1.22 (1.00-1.50)
current (n=40)	1.10 (0.82-1.48)	**0.53 (0.34-0.83)**	**0.75 (0.63-0.89)**	1.29 (1.00-1.66)
	P het =0.531	***P* het = 0.020**	***P* het = 0.001**	*P* het =0.071

a) Spearman partial correlation (r) or logistic regression (OR and 95% CI, per 10 units increase in biomarker), adjusted for sex and age at recruitment; **b)** HbA1c (glycated hemoglobin) values were available for 103 out of the 217 controls (47%) and for 120 out of the 157 cases (76%)**; c)** self-reported at baseline

Supplemental Table S2: Sensitivity at 95% and 98% specificity for detection of histologically confirmed pancreatic cancer cases (N=106), for crude marker measurements by time between blood draw and diagnosis.

lag time	cases	threshold 95% sp	SE95 (95%-CI)	threshold 98% sp	SE98 (95%-CI)
ApoA2 –ATQ/ AT					
full sample	**106**	32.60	0.16 (0.08-0.30)	26.60	0.08 (0.03-0.23)
<= 6months	**11**	32.60	0.27 (0.08-0.61)	26.60	0.18 (0.04-0.56)
>6 -18months	**17**	32.60	0.35 (0.15-0.63)	26.60	0.24 (0.07-0.55)
<=18months	**28**	32.60	0.32 (0.15-0.56)	26.60	0.21 (0.07-0.48)
CA19-9					
full sample	**106**	27.80	0.20 (0.10-0.35)	42.00	0.12 (0.05-0.29)
<= 6months	**11**	27.80	0.55 (0.24-0.82)	42.00	0.45 (0.17-0.77)
>6 -18months	**17**	27.80	0.29 (0.11-0.58)	42.00	0.24 (0.07-0.55)
<= 18months	**28**	27.80	0.39 (0.20-0.62)	42.00	0.32 (0.14-0.59)

Note: sp=specificity; SE95 = sensitivity at 95% specificity; SE98 = sensitivity at 98% specificity; CI = confidence interval; comparisons to 144 controls.

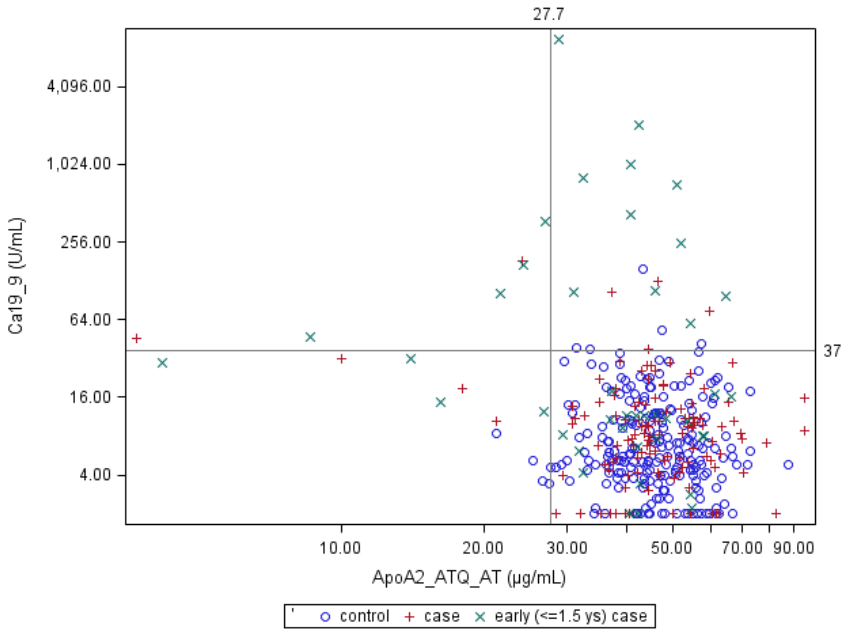


Supplemental Figure S1. ApoA2-ATQ/ATQ *vs.* ApoA2-AT/AT (crude values) for control subjects and pancreatic cancer cases, by lag-time from blood donation till diagnosis of (matched) case.

Among both pancreatic cancer cases and cancer-free controls, plasma levels of the ApoA2-AT/AT ("light") and ApoA2-ATQ/ATQ ("heavy") isoforms show an inverse, convex relationship. Especially among the cases, sub-sets display either high ApoA2-AT/AT combined with low ApoA2-ATQ/ATQ ("hyper-processors), or high ApoA2-ATQ/ATQ with low ApoA2-AT/AT ("hypo-processors"). At a given overall concentration of the Apo2i isoforms combined, more imbalanced ratios of ATQ/ATQ *vs*. AT/AT homodimers result in lower calculated values for the ATQ/AT heterodimer, which can be estimated using the equation

$$\mathrm{ApoA2-ATQ/AT\ (\mu g/ml)} = \sqrt{(apoA2\_ATQ\_ATQ * apoA2\_AT\_AT)}$$

and which are used as the summary ApoA2i index for pancreas cancer detection.

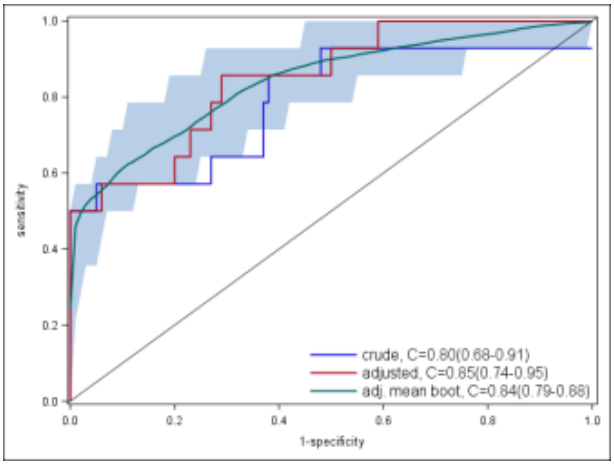


Supplemental Figure S2. Scatterplot of CA19-9 and and ApoA2-ATQ/AT biomarker values for control subjects (circles) and pancreatic cancer cases (crosses).
Green crosses represent cases diagnosed within ≤18 months after blood draw, red crosses represent those diagnosed after longer time intervals.

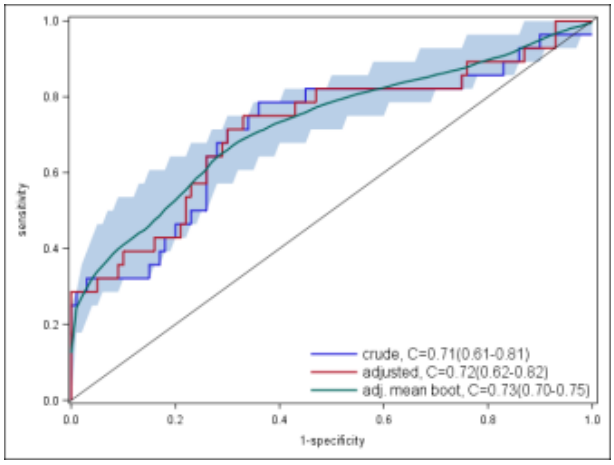
Supplementary Figure S3: Crude ROC curves, adjusted ROC-curves and average adjusted ROC-curve after bootstrapping with empirical confidence region for markers and time-slots

Ca19-9

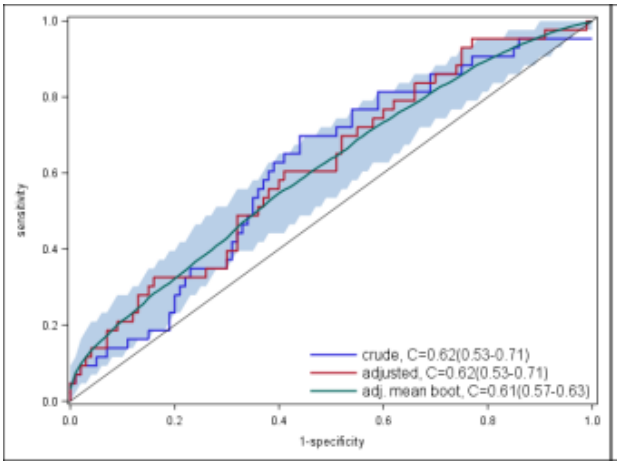
<=6 months



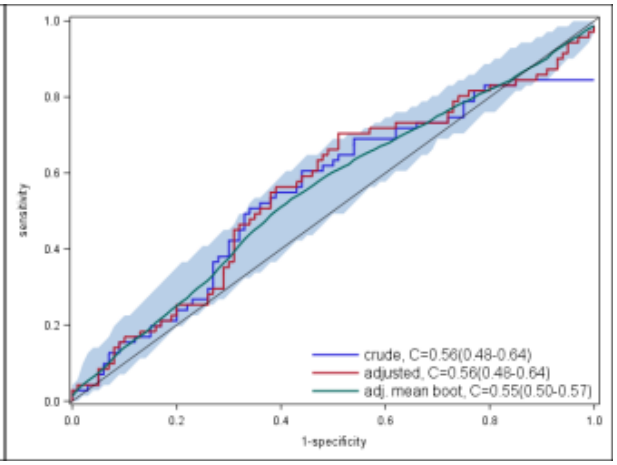
>6, <=18 months



>18, <=36 months

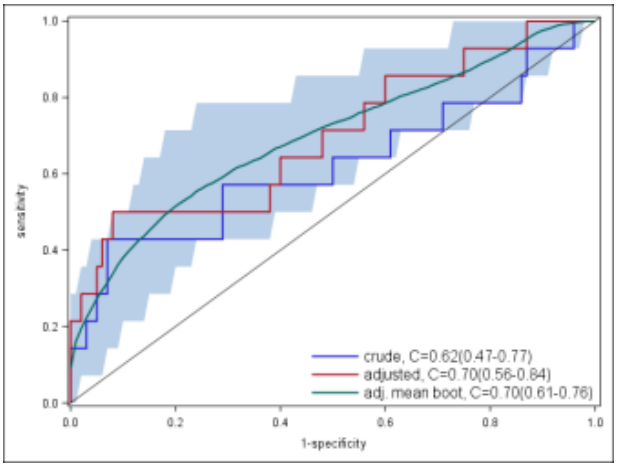


>36 months

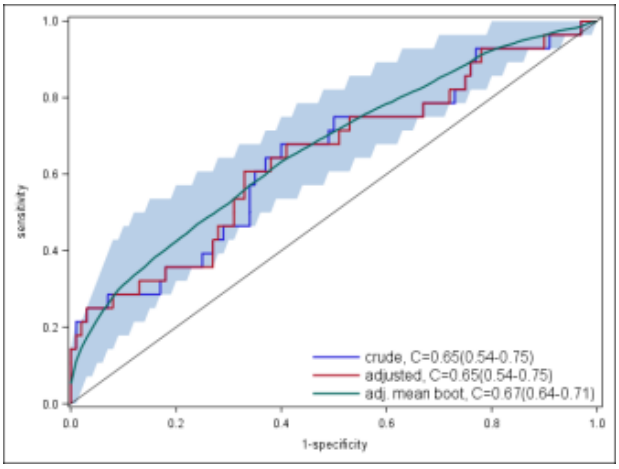


ApoA2-ATQ/AT

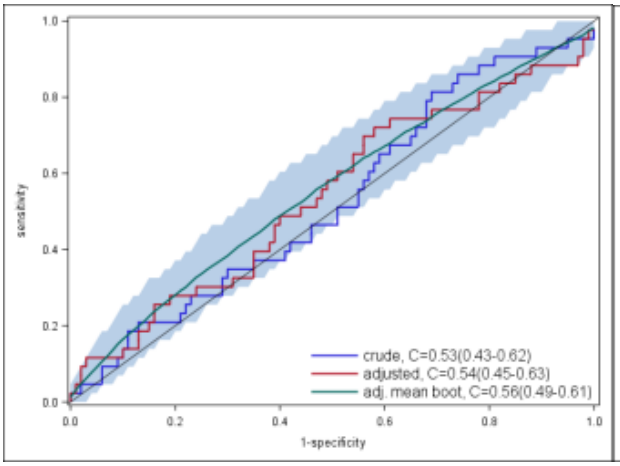
<=6 months



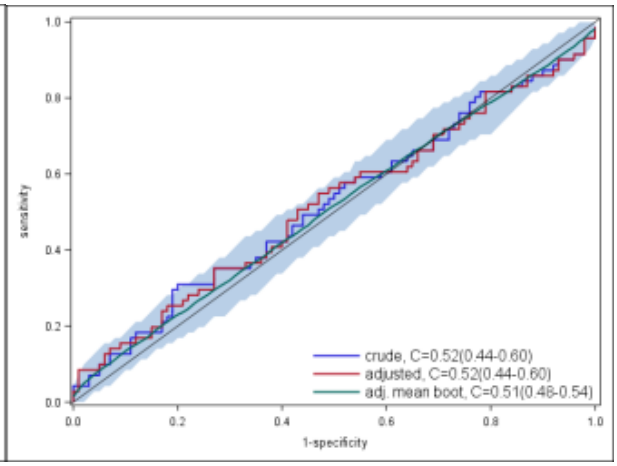
>6, <=18 months



>18, <=36 months

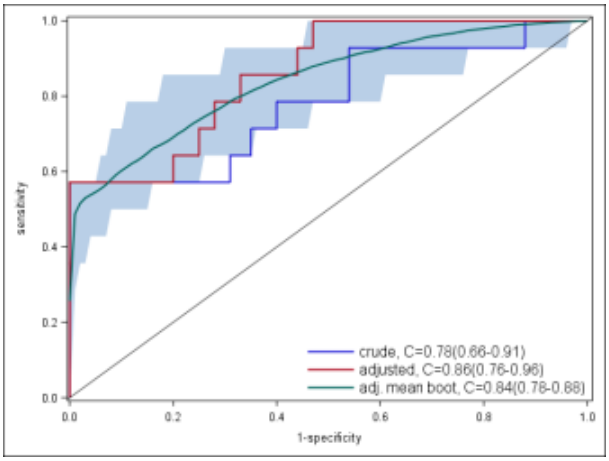


>36 months

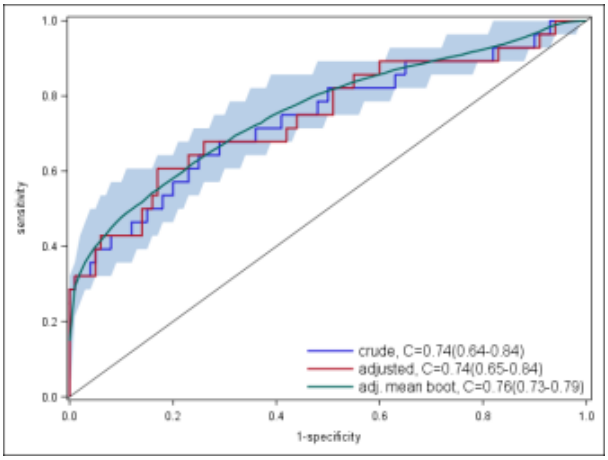


CA19-9 and ApoA2-ATQ/AT

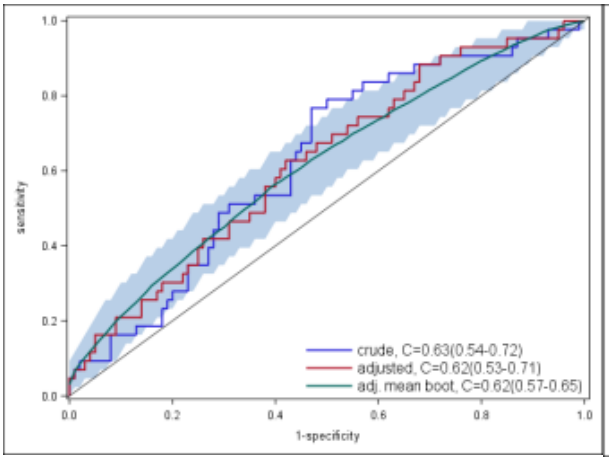
<=6 months



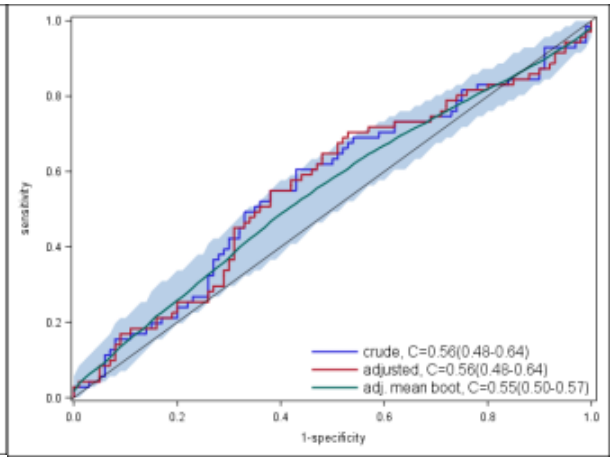
>6, <=18 months

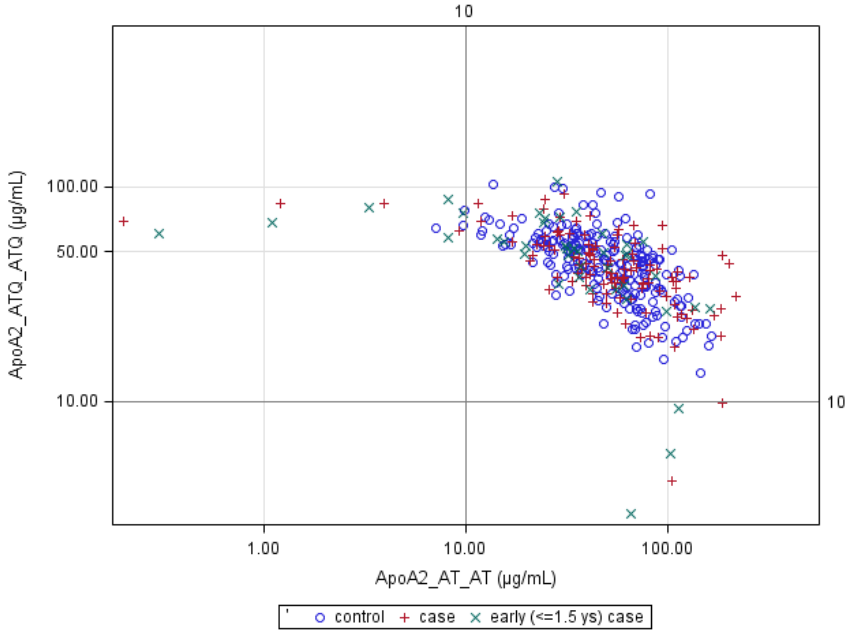


>18, <=36 months



>36 months





Supplemental Figure S4. Scatterplot of ApoA2-ATQ/ATQ and ApoA2-AT/AT homomer values of control subjects (circles) and pancreatic cancer cases (crosses).

Green crosses represent cases diagnosed within ≤18 months after blood draw, red crosses represent those diagnosed after longer time intervals.

Supplemental Methods

EPIC cohort

In brief, 519,978 women and men, mostly aged 35-70 years (40-70 for men) were enrolled between 1992 and 2000 in 23 centers in 10 European countries: Denmark, France, Germany, Greece, Italy, Norway, the Netherlands, Spain, Sweden, and the United Kingdom. Participants were recruited from the general population in the local geographic areas (towns and provinces), with exception of the French cohort which recruited participants through a national health insurance plan for teachers, parts of the Italian and Spanish cohorts in which participants were recruited from among blood donors, and most of the Oxford cohort which recruited mainly health-conscious participants, including vegetarians. In Utrecht and Florence the cohorts consisted of women attending local, population-based breast cancer screening programs.

At baseline, all study participants provided comprehensive questionnaire data on diet, lifestyle, reproductive and menstrual factors, current and past use of exogenous hormones [oral contraceptives (OC) and postmenopausal hormone replacement therapy (HRT)] and medical history. In addition, anthropometric measures were obtained. Finally, about 80 per cent of the EPIC participants (226,673 women and 159,074 men) also provided a baseline blood sample, which was further processed into aliquots of serum, plasma, red blood cells and buffy coat [26]. All participants gave their consent for future analyses of their blood samples and the current study was approved by the IARC Ethics Committee and the Institutional Review Boards of local EPIC centers.

Follow-up for cancer incidence and vital status

Incident cancer cases are identified by population cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the UK) or by a combination of methods including health insurance records, cancer and pathology registries and active follow-up of study

participants (France, Germany, Greece). Detailed information on tumor characteristics (tumor morphology code; grade [well, moderately, or poorly/undifferentiated]; and stage [local, regional, metastatic]) is obtained from cancer registries, complemented with pathology reports obtained from treating clinics. All incident cases of cancer are coded according to the International Classification of Diseases for Oncology (ICD), version 10. Parallel to the prospective cancer ascertainment, in all EPIC centers vital status is determined by regular linkages with population and mortality registers at the regional or national level.