



Acides gras et cancer du sein: application de biomarqueurs

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International Agency for Research on Cancer
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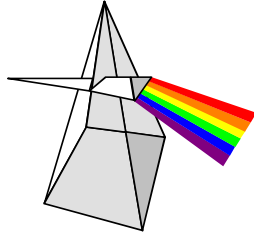
Outline

- Fatty acids: biochemistry, metabolism in cancer and functions in cellular processes
- Dietary intake of fatty acids and breast cancer: epidemiology
- Lipidomics in cancer: What type of biomarkers?
- Fatty acids and breast cancer: application of biomarkers

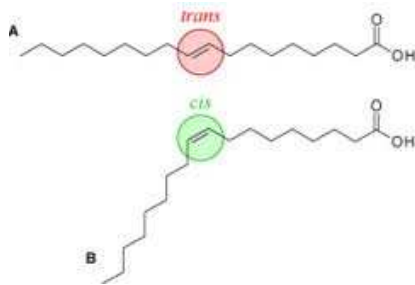
- Discussion
- Research perspectives

Complexity of lipids

Lipids



Triacylglycerides
Phospholipids
Sterols
Sphingolipids
Fatty acids



From diet

ω-6 PUFA	ω-3 PUFA
linoleic 18:2	α -linolenic 18:3
arachidonic 20:4	EPA 20:5
	DHA 22:6

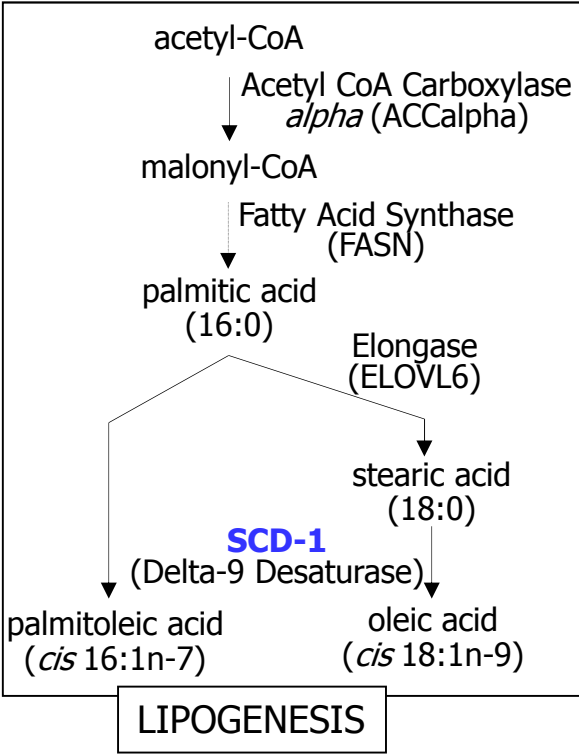


From diet and metabolism

Saturates
Monounsaturates
cis/trans



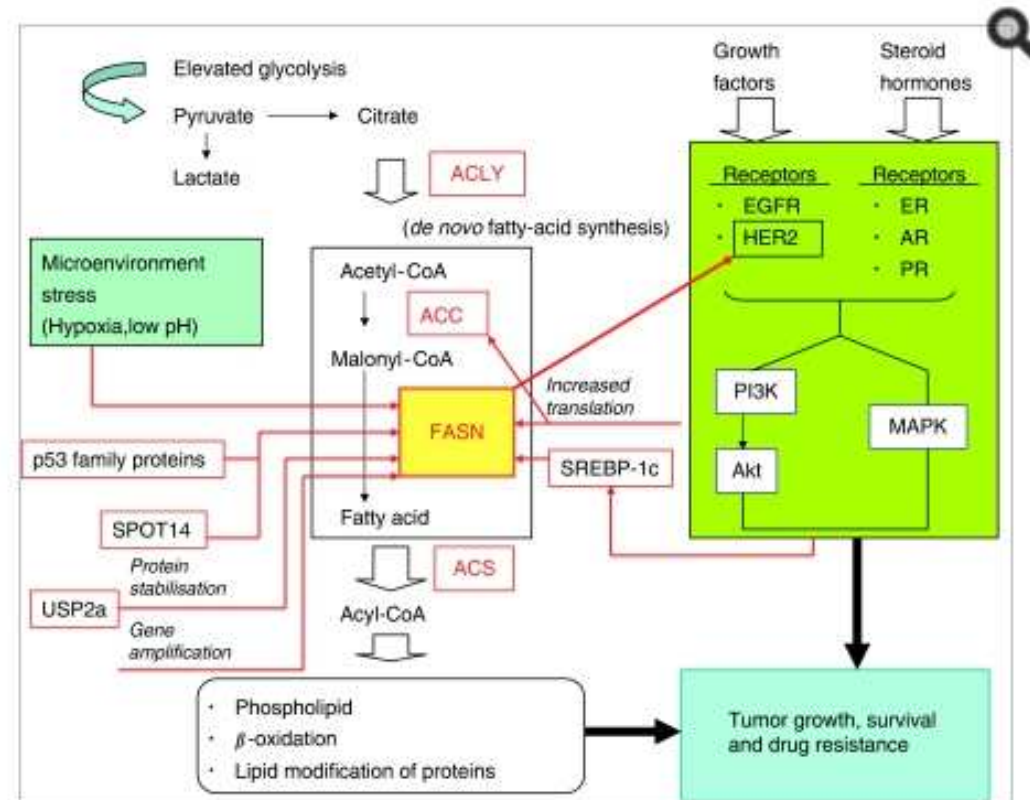
PUFA
cis/trans



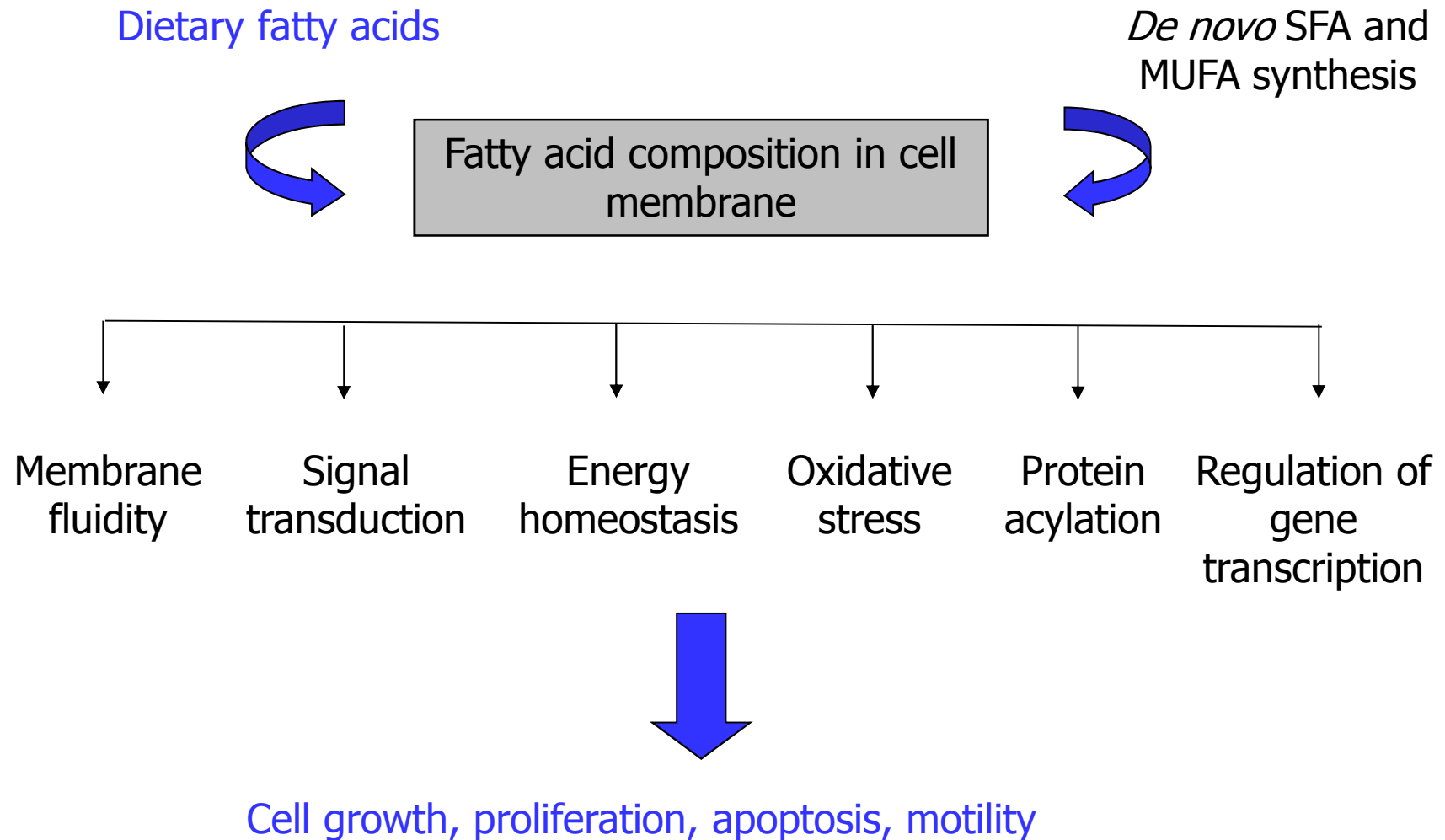
Alteration of fatty acid synthesis in cancer cells

- Elevated glycolysis for ATP production (Warburg effect)
- Increased *de novo* fatty acid synthesis (*FAS*, *ACC*, *SCD-1*) is essential:
 - ✓ to support increased membrane biosynthesis
 - ✓ to support increased energy need;
 - ✓ to breast cancer cell growth and survival

(Chajès et al, Cancer Res 2006)



Fatty acids: functions in cellular processes



Dietary intake of fatty acids and breast cancer: epidemiology

- Components of fat (FFQ)
- Total fat
- Saturated fatty acids

} possible increased risk

Dietary intake of fatty acids and breast cancer: epidemiology

- Components of fat (FFQ)
 - Total fat
 - Saturated fatty acids
- } possible increased risk
- Monounsaturated fatty acids (*cis*)
diverging associations
 - Polyunsaturated fatty acids
 - ω 6 PUFA null or positive associations
 - ω 3 PUFA null or negative associations
- } → evidence less clear

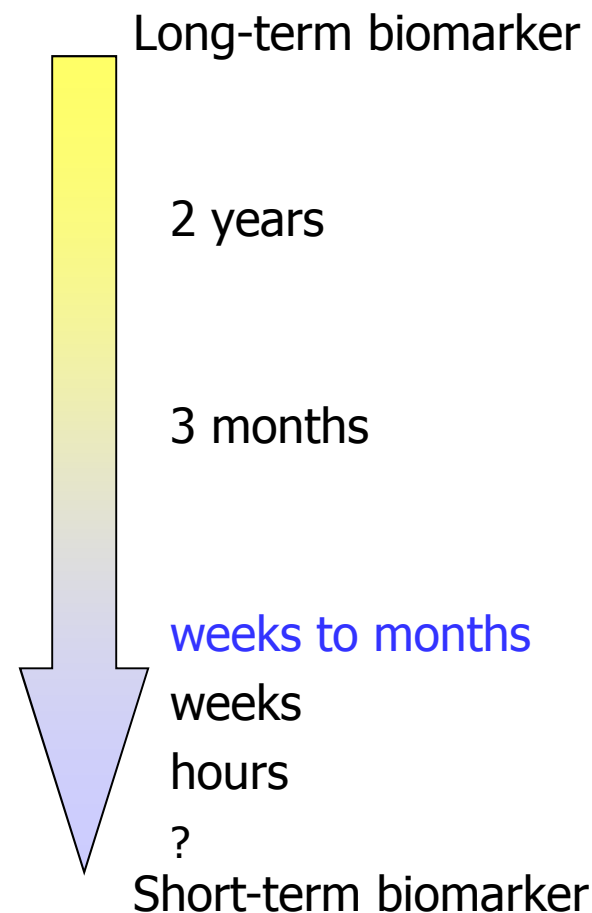
Fatty acids and breast cancer: discrepancies

❖ Unresolved issues:

- Confounding by energy intake
- Exposure misclassification
 - recall bias in case-control studies
 - measurement error in dietary fat assessment
- Homogeneous populations
- Interactions
 - dietary factors (antioxidants....)
 - genetic polymorphisms
- Hormonal receptor status

Lipidomics in cancer. What type of biomarkers?

- Adipose tissue (gluteal, breast, etc.)
 - Triglycerides
- Erythrocytes or platelets
 - Membrane phospholipids
- Lipid fractions in serum or plasma
 - Phospholipids
 - Cholesterol esters
 - Triglycerides
 - Total serum



Fatty Acids and Cancer Risk: overall strategy based on biomarkers

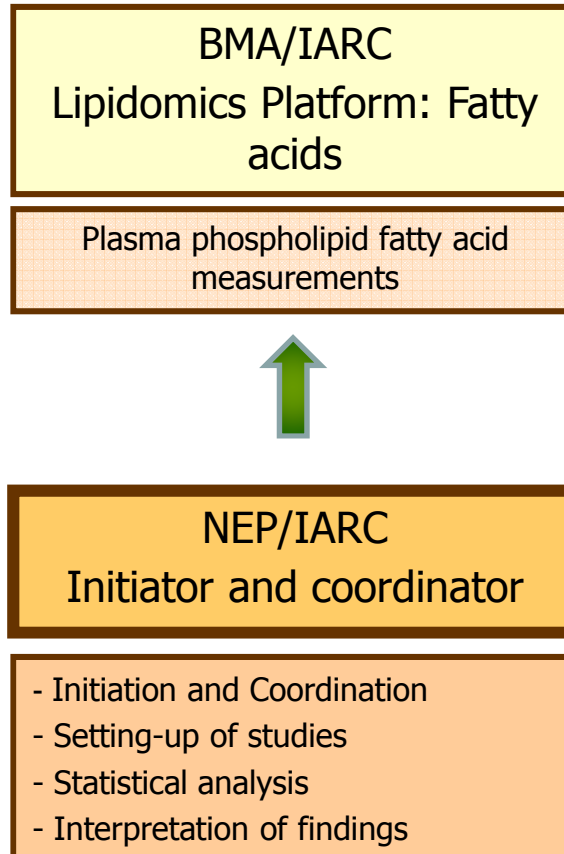
Current hypotheses on fatty acids and breast cancer risk:

Diet

- Impact of unbalanced ratios between fatty acids
- Protective effect of ω -3 PUFAs
- Promoting effect of industrial *trans* fatty acids

Metabolism

- Promoting effect of endogenously synthesized MUFA



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Fatty Acids and Cancer Risk: overall strategy based on biomarkers

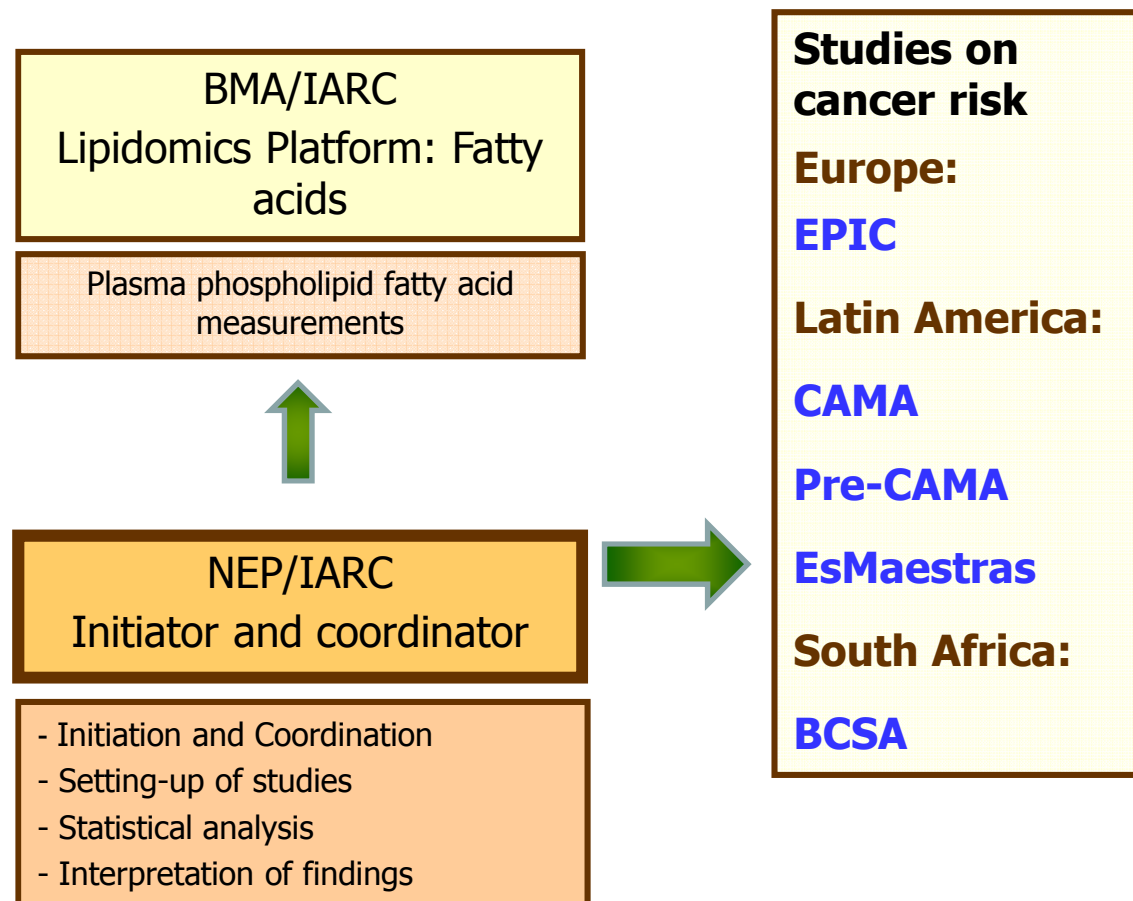
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Fatty Acids and Cancer Risk: overall strategy based on biomarkers

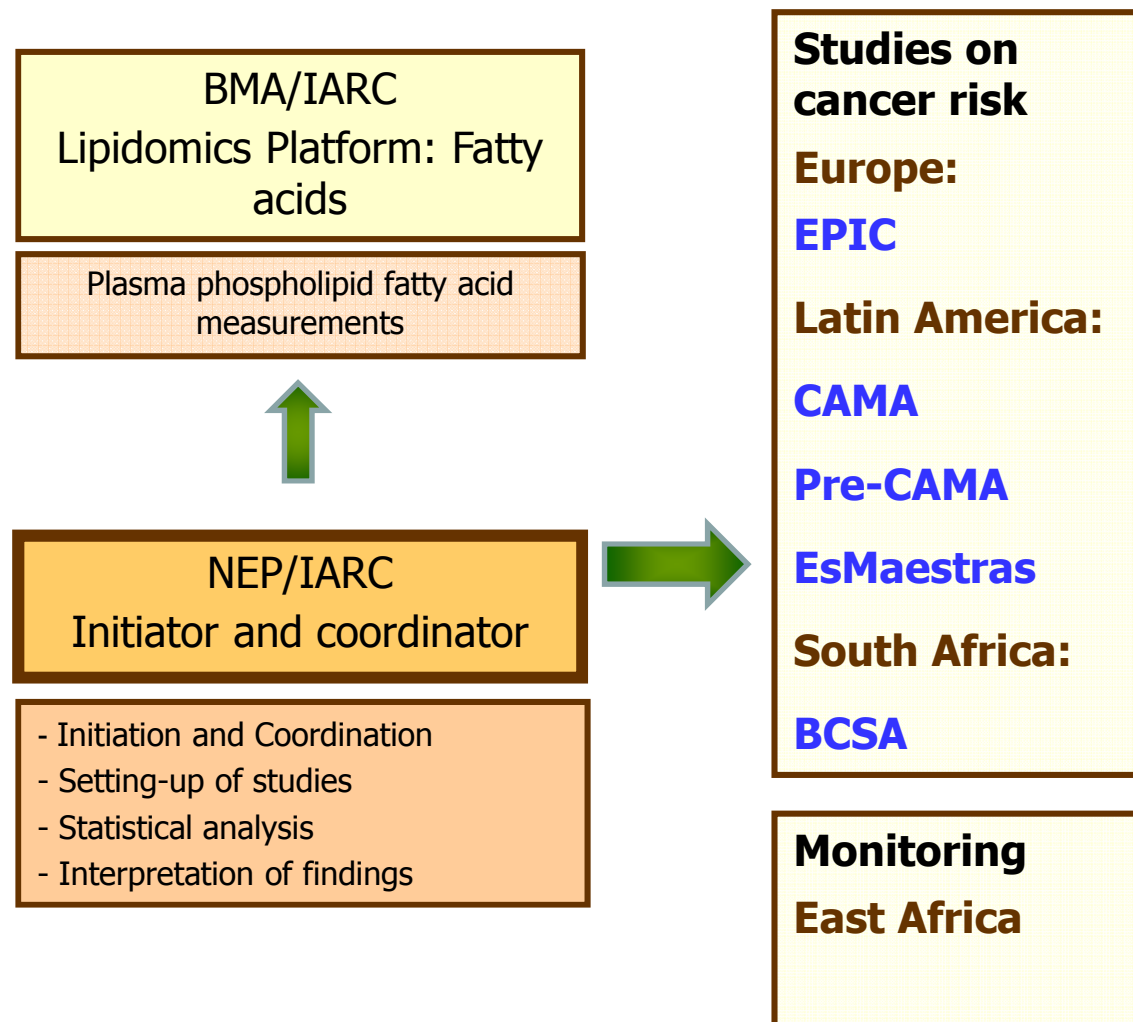
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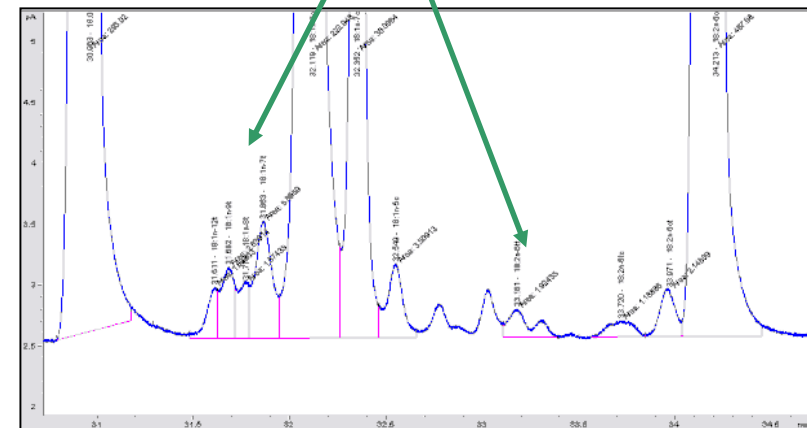
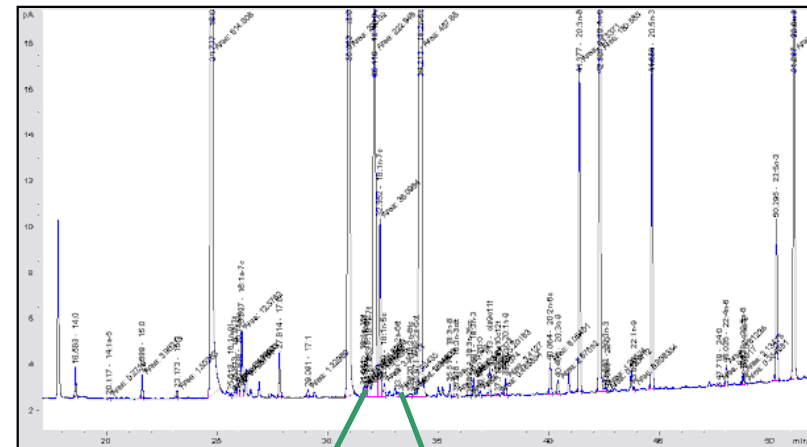
Analytical method development

Setting up of a novel analytical method on GC/FID to measure 60 plasma phospholipid fatty acids:

- SFA
- *cis* MUFA
- Industrial vs ruminant *trans* MUFA
- *cis* ω -6 PUFA
- Industrial vs ruminant *trans* ω -6 PUFA (18:2 *trans* isomers, CLA)
- *cis* ω -3 PUFA
- *trans* ω -3 PUFA (18:3)

- Ratio MUFA/SFA = desaturation index
- Balance between PUFA

60 fatty acids in plasma phospholipids, including 15 *trans* fatty acid isomers



Fatty acids and breast cancer: recent data based on biomarkers

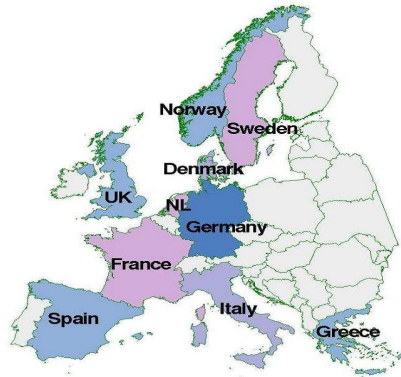
1. The European EPIC cohort study: biomarkers of fatty acids
2. The Mexican CAMA case-control study: biomarkers of fatty acids

Cohort Study: EPIC

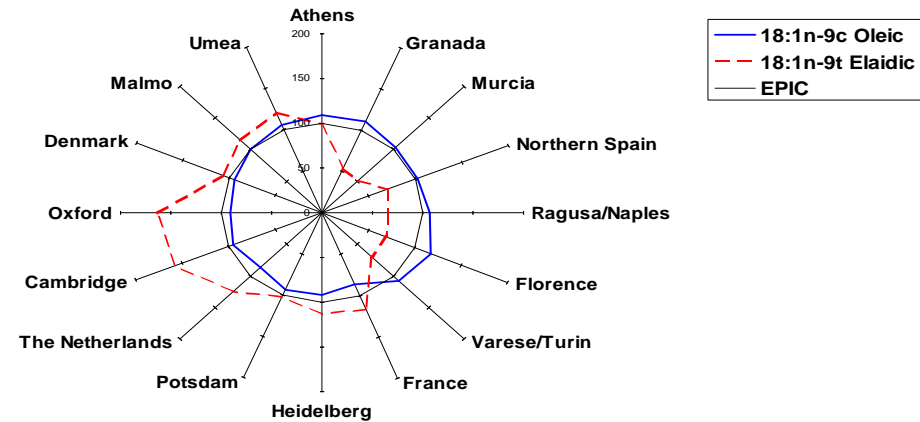
- 12.5 years of follow-up on average
- 6.5 million Person-years
- 47,525 incident cancer cases
- 36,977 incident deaths
- 32,070 incident diabetes and CVD
- 8,552 subjects with more than one incident morbid condition



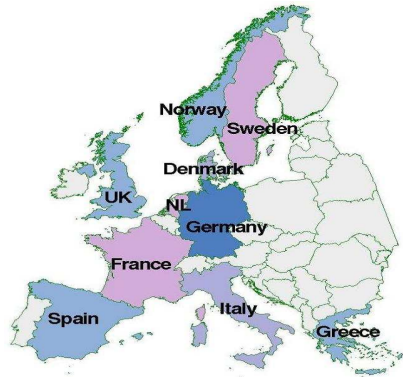
Validation of biomarkers: elaidic acid



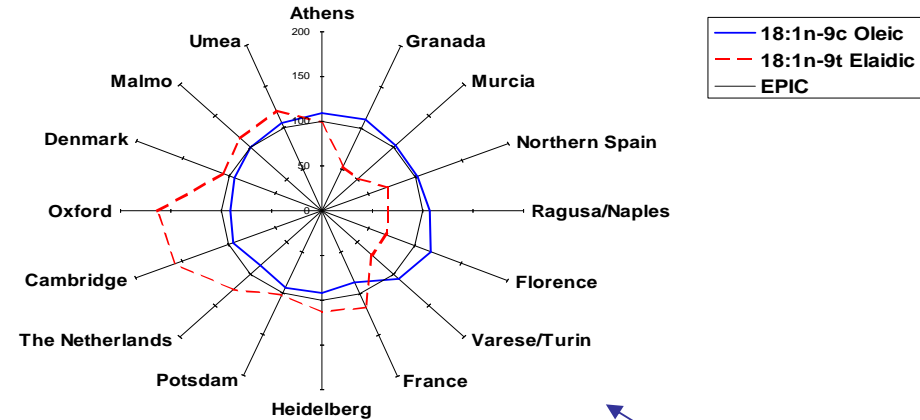
Calibration study, 24HDR,
3,000 subjects



Validation of biomarkers: elaidic acid



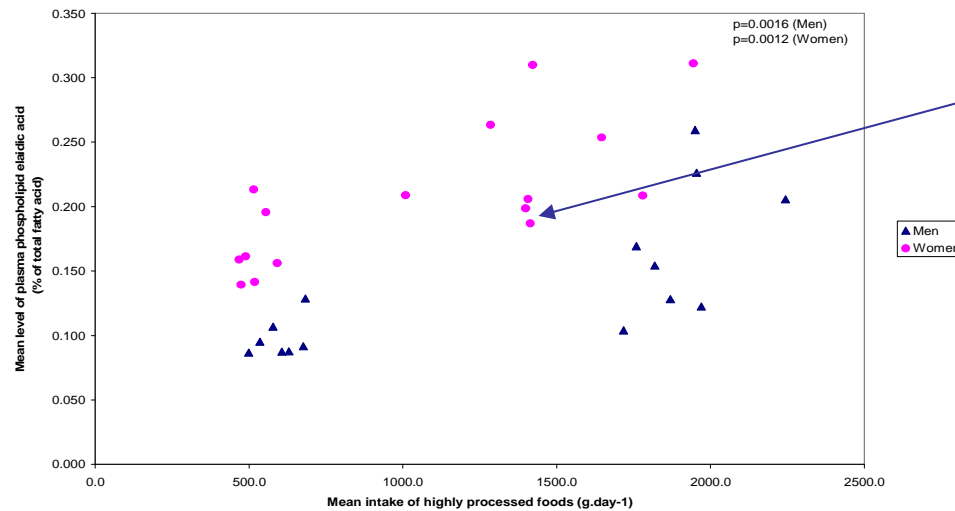
Calibration study, 24HDR,
3,000 subjects



Industrial foods



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E3N

(Chajès et al, Nutr cancer 2011)

Biomarkers and breast cancer: design



The EPIC cohort study

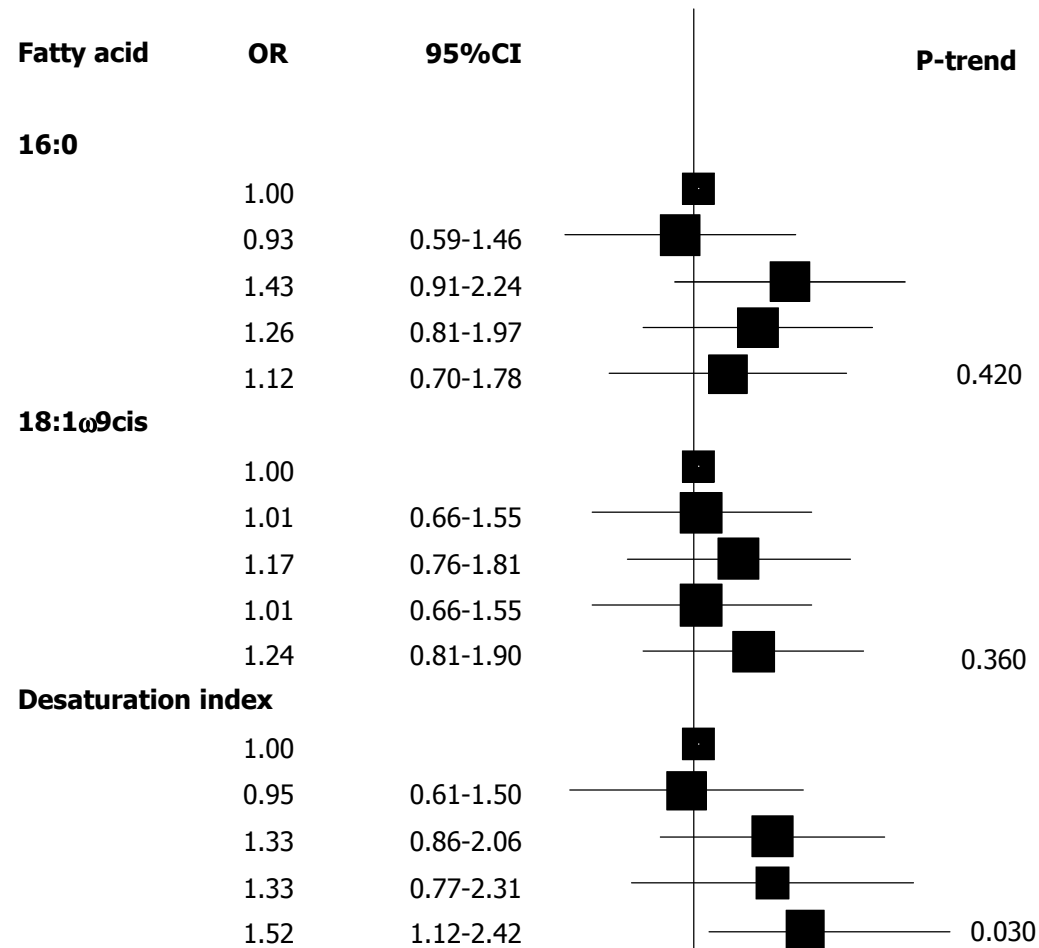
521,468 subjects
(1992-2000)

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- Study population:
 - ✓ 5,000 breast cancer cases (FFQ, blood samples) within EPIC;
 - ✓ One control matched on age, menopause, center and date at blood collection
- GC-FID measurements of plasma phospholipid fatty acids **on-going** (IGR, IARC)
- Statistical analysis
 - ✓ Conditional logistic regression
 - ✓ Adjustment for risk factors of breast cancer (years of education, BMI, adult height, menopausal hormone use, alcohol consumption, age at first birth and parity, family history of breast cancer, personal history of benign breast disease)
 - ✓ Data presented for France (700 cases)

Saturates, monounsaturates, desaturation index

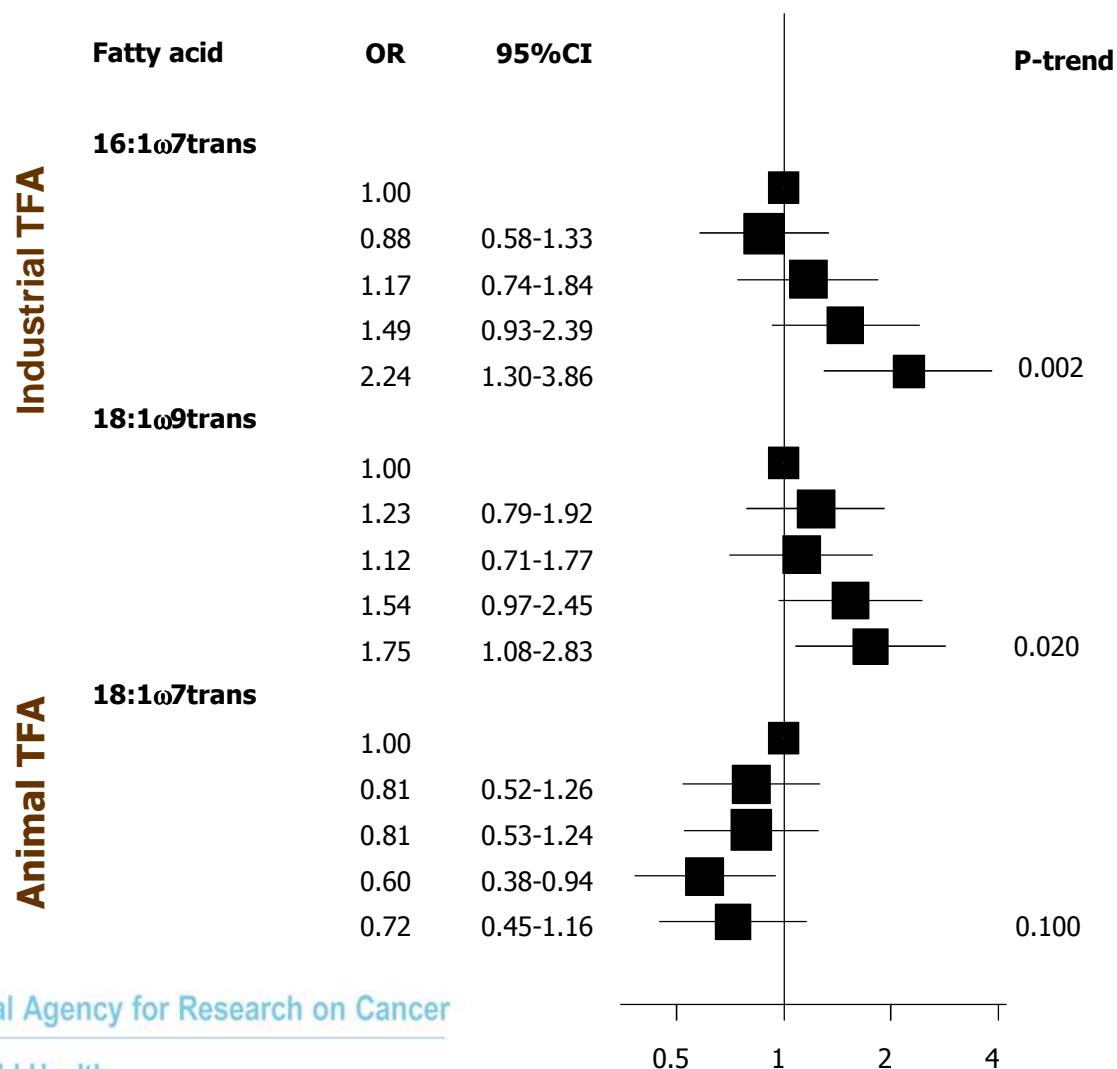


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(Chajès et al, on-going study)

Trans fatty acids

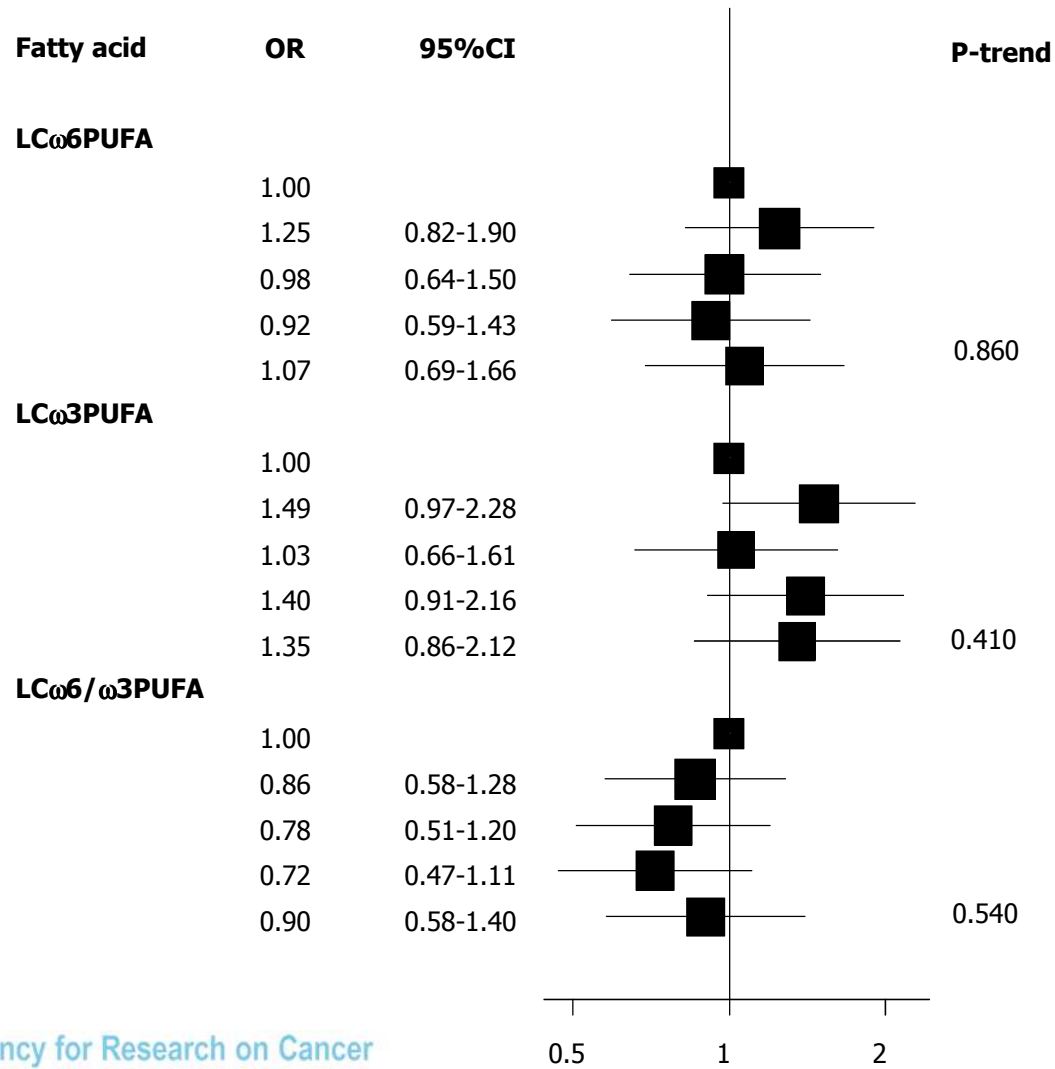


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(Chajès et al, on-going study)

ω6 and ω3 PUFA



Fatty acids and breast cancer: recent data based on biomarkers

1. The European EPIC cohort study: biomarkers of fatty acids
2. The Mexican CAMA case-control study: biomarkers of fatty acids

Design

Multicenter, case control CAMA study (2004-2007)



1,000 breast cancer cases

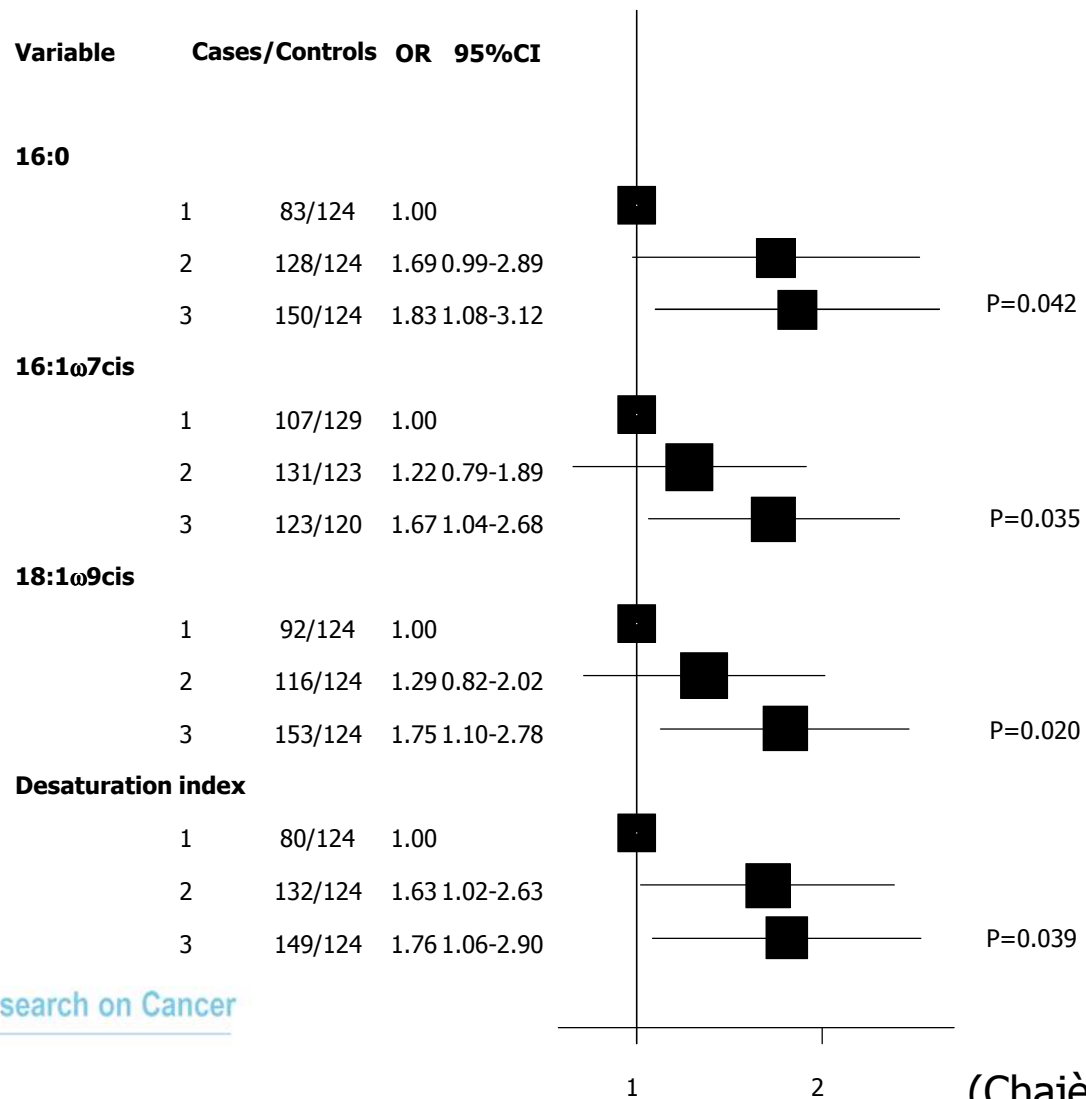
1,074 controls

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- Study population:
 - ✓ 400 breast cancer cases (FFQ, blood samples)
 - ✓ 400 controls frequency matched to cases according to age, health-care system and region
- Measurements of plasma phospholipid fatty acids through GC-FID at IARC/BMA
- Statistical analysis
 - ✓ Conditional regression model
 - ✓ Adjustment for risk factors of breast cancer (years of education, BMI, adult height, menopausal hormone use, alcohol consumption, age at first birth and parity, family history of breast cancer, personal history of benign breast disease)

Saturates, monounsaturates, desaturation index



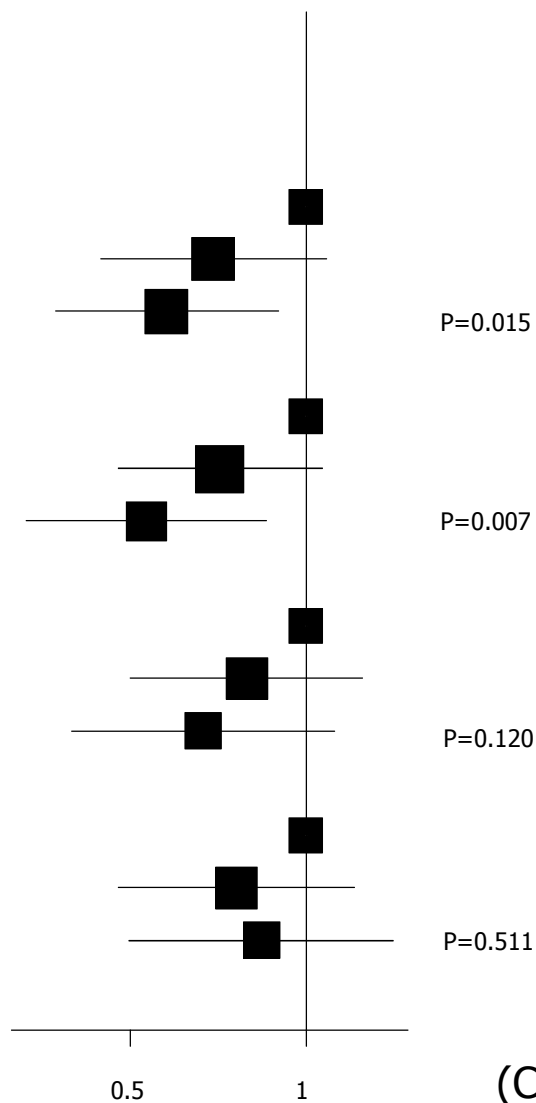
(Chajès et al, ms in prep)

Trans fatty acids

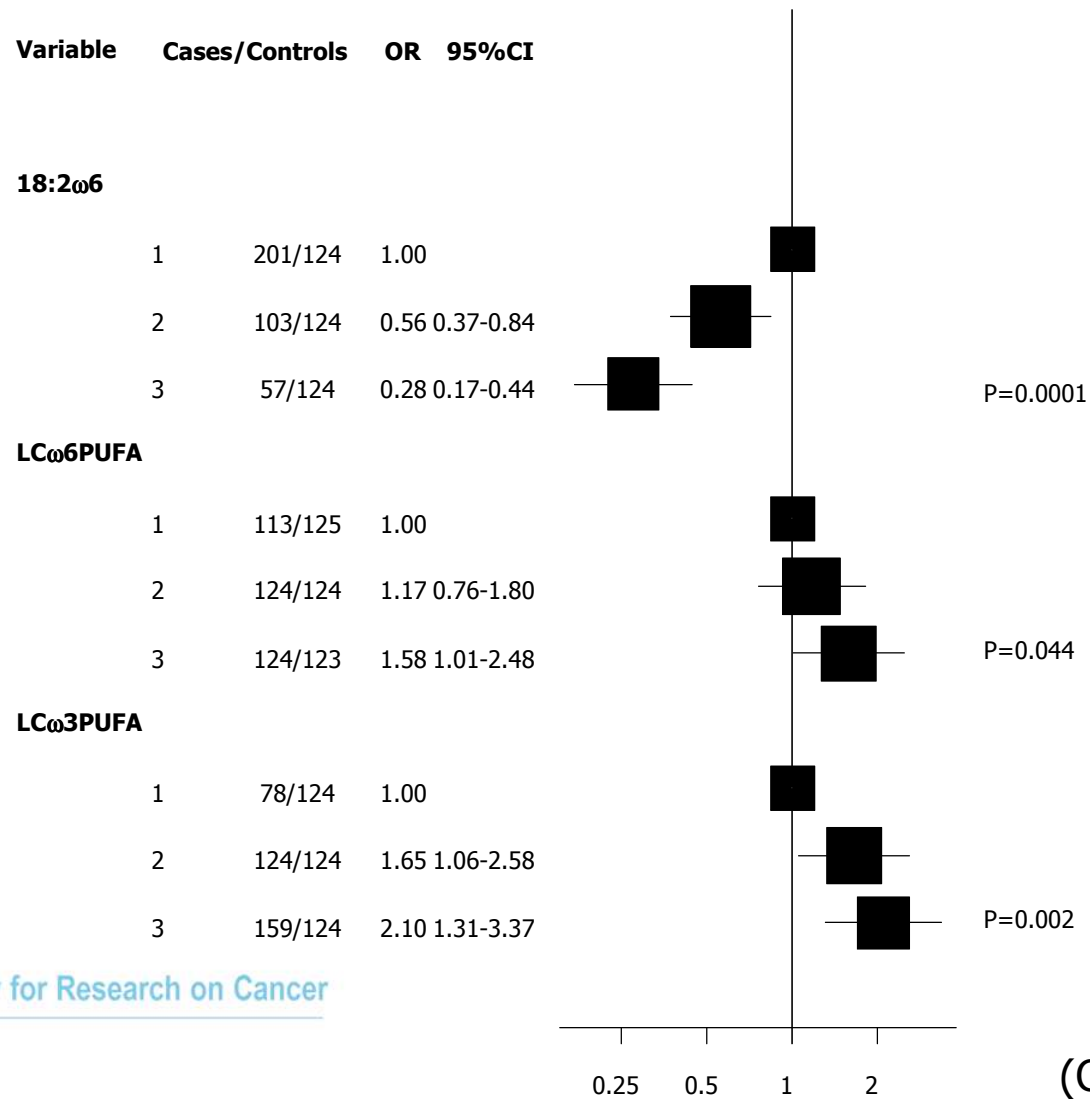
Industrial TFA

Animal TFA

Variable	Cases/Controls	OR	95%CI
16:1ω7 trans			
1	139/126	1.00	
2	109/123	0.69	0.44-1.08
3	113/123	0.58	0.37-0.90
18:1ω9 trans			
1	183/128	1.00	
2	122/153	0.71	0.48-1.06
3	56/91	0.53	0.33-0.86
ω6PUFA trans			
1	137/136	1.00	
2	127/131	0.79	0.50-1.25
3	97/105	0.67	0.40-1.12
18:1ω7 trans			
1	132/127	1.00	
2	107/127	0.76	0.48-1.21
3	122/118	0.84	0.50-1.41



ω 6 and ω 3 PUFA



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(Chajès et al, ms in prep)

Discussion: main results on biomarkers

The prospective E3N-EPIC cohort study

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Discussion: main results on biomarkers

The prospective E3N-EPIC cohort study

Desaturation index

- ✓ High intake of saturated fatty acid
- ✓ Increased desaturation of SFA, increased hepatic expression of SCD-1 may increase breast cancer risk

Discussion: main results on biomarkers

The prospective E3N-EPIC cohort study

Desaturation index

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Biomarkers of dietary exposure: industrial *trans* fatty acids

- ✓ A high intake of ITFA may increase breast cancer risk
- ✓ Mechanistical data? Oxidative stress?

Discussion: main results on biomarkers

The prospective E3N-EPIC cohort study

Desaturation index

- ✓ High intake of saturated fatty acid
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Biomarkers of dietary exposure: industrial *trans* fatty acids

- ✓ A high intake of ITFA may increase breast cancer risk
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Biomarkers of dietary exposure: ω 3 PUFA

- ✓ Minimal intake required to see a protective effect?
- ✓ Effect dependent on ITFAs, antioxidants?

Discussion: main results on biomarkers

The CAMA case-control study

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Discussion: main results on biomarkers

The CAMA case-control study

Desaturation index

- Increased desaturation of SFA, increased hepatic expression of SCD-1

Discussion: main results on biomarkers

The CAMA case-control study

Desaturation index

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Biomarkers of dietary exposure: industrial *trans* fatty acids and ω 3 PUFA

- Do not reflect past dietary intake in a case-control design but an effect of tumor progression on plasma levels

Discussion: main results on biomarkers

The CAMA case-control study

Desaturation index

- Increased desaturation of SFA, increased hepatic expression of SCD-1

Biomarkers of dietary exposure: industrial *trans* fatty acids and ω 3 PUFA

- Do not reflect past dietary intake in a case-control design but an effect of tumor progression on plasma levels
- Opposite effect depending on tumor stage?

Research perspectives: application of biomarkers

- **Application of biomarkers** for monitoring dietary fatty acid changes over time **in low to middle income countries:**
 - ✓ South Africa
 - ✓ East Africa
- **Application of biomarkers** of fatty acids in relation to **breast cancer risk in low to middle income countries:** collaborative studies
 - ✓ Latin America
 - ✓ South Africa
 - ✓ East Africa
- **Application of biomarkers** of fatty acids in relation to **cancer risk** in the EPIC cohort
 - ✓ Pancreatic cancer
 - ✓ Adenoma and colorectal cancers

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BMA

DEX

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