# Breast cancer prevention: what is known and gaps in knowledge

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Breast Cancer in Latin America

Estimated age-standardised incidence and mortality rates: women

Globocan 2008
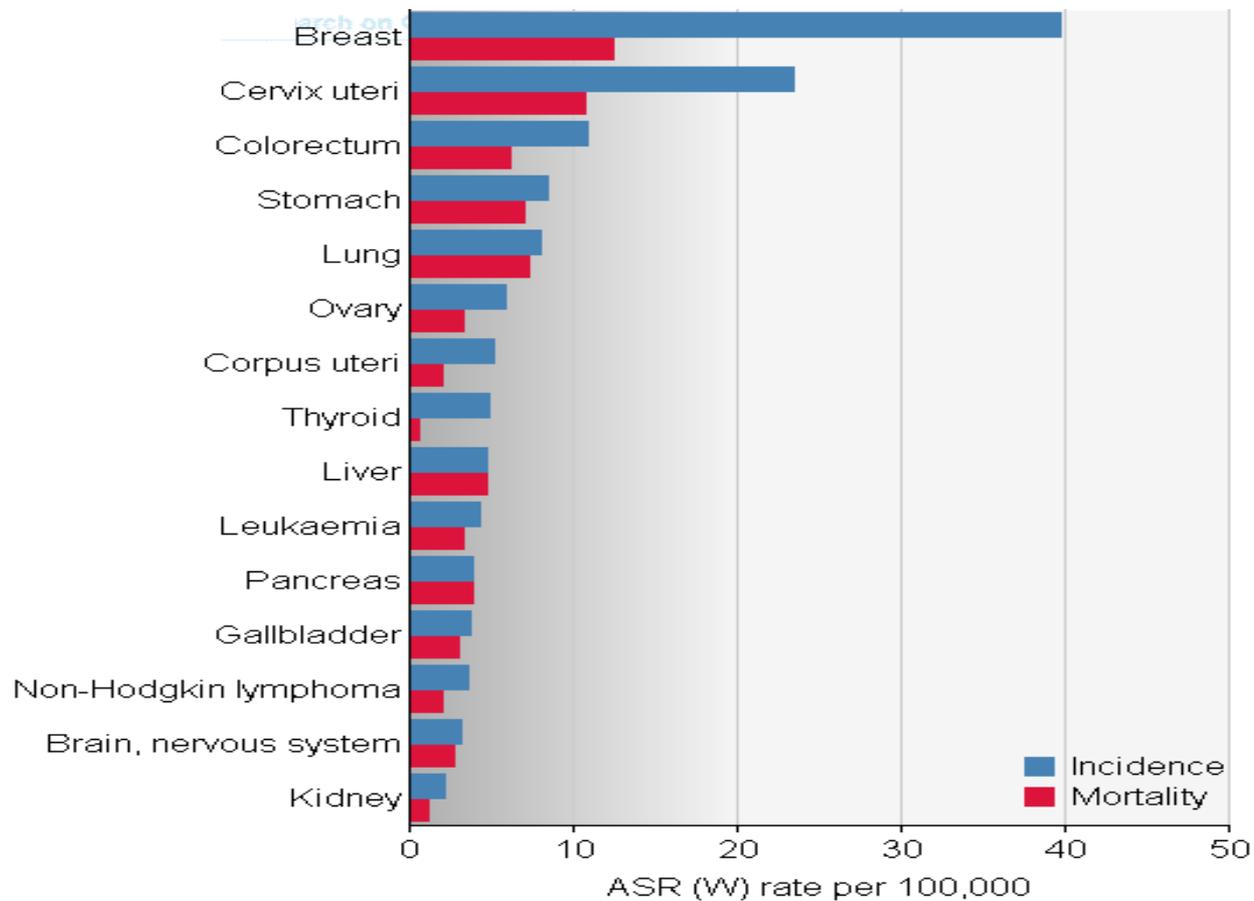
Breast Cancer: A *new Epidemic?*

- **Reproductive pattern has changed:**
    - **later age at first pregnancy**
    - **Decrease in parity**
    - **Decrease in duration of breastfeeding**

- **Rapid changes in life syle** **in particular nutritional habits with large increase in obesity**

- **Amerindian population** **has a great risk of diabetes which could be related to breast cancer**

- **The high consumption of carbohydrate** **can worsen the susceptibility to diabetes and to BC**

Estimation of number of cases of Diabetes Mellitus

- **Estimation of an increase of Mellitus Diabetes from *135 millions to 300 millions in 2025.***

- **The increase will be more important in LDC**

1000000

100000

10000

1000

- World
- Developed countries
- Developing countries
- Mexico

1995   1997   2000   2025

NMH/DIA. Diabetes Estimates 1995 - 2025. Geneve, Switzerland: World Health Organization, 2001
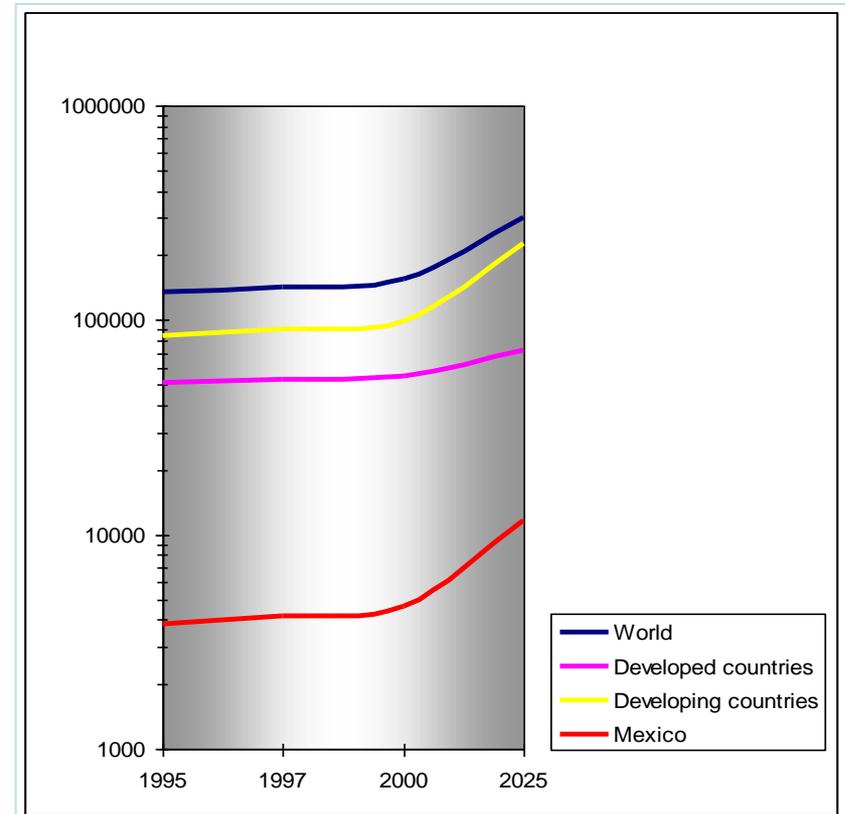
Insulin resistance/ Diabetes and Breast Cancer: CAMA-Mexico

	Premenopausal [*]			Postmenopausal [†]		
	OR	95% CI		OR	95% CI	
Diabetes						
No	1.0			1.0		
Yes	1.6	0.9 - 2.9		2.5	1.7 - 3.7	
Moderate-intensity physical activity (hours per week)						
?5 hrs/week	1.0			1.0		
5 - 19 hrs/week	1.3	0.9 - 2.0		0.7	0.5 - 1.1	
>19 hrs/week	0.5	0.4 - 0.8		0.3	0.2 - 0.5	
p for trend		p=0.002		p<0.001		

Premenopausal Breast cancer

	Case	Control	OR[a]	95% CI		OR[b]	95% CI	
Diabetes								
No	197	270	1.0			1.0		
Yes	17	19	1.1	0.6 - 2.3		1.1	0.4 - 2.7	
C Peptide (ng/mL)								
≤ 1.2	54	106	1.0			1.0		
1.3 -2	64	110	1.2	0.7 - 1.9		1.5	0.8 - 2.7	
2.1 - 7.2	115	92	2.7	1.7 - 4.2		5.7	2.9 - 11.0	

Multivariate model adjusted, by design, for 5-year age range, health institution and site, plus other variables such as: being told by a physician of having diabetes mellitus, socioeconomic status, body mass index, waist-hip index, parity, history of breast cancer (mother-sister), ever use of oral contraceptives, age at menarche, occasional intake of > 1 alcohol drinks per mo during ≥ 1 year (yes/no), moderate physical activity (hours per week), energy intake (kcal/day), and variables included in the table.

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Torres-Mejia G 2012

Breast Cancer Risk

Not modifiable:

- Genetics/family history
- Age
- Race/ethnicity
- Height
- Age at menarche

Modifiable:

- Diet
- Body mass index
- Exercise
- Smoking
- Exogenous estrogen use
- Alcohol consumption
- Breastfeeding

Potentially modifiable:

- Age at first birth

IARC Handbook of Cancer Prevention. Vol 6: Weight Control and Physical Activity, 2002

WCRF/AICR Report on Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective, 2007

anses
agence nationale de sécurité sanitaire
alimentation, environnement, travail

Nutrition et cancer

Rapport d'expertise collective

Mai 2011   Édition scientifique

IARC Handbooks of Cancer Prevention

International Agency for Research on Cancer
World Health Organization

Weight Control and Physical Activity
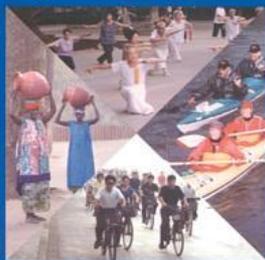
Volume 6

IARC Press
2002

World Cancer Research Fund   American Institute for Cancer Research

Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective

International Agency
World Health Organization

Nutrition- Energy Balance and Breast Cancer
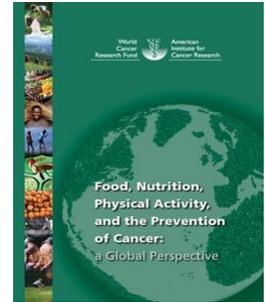
- **Factors that modify the risk of BC in _premenopausal_ women:**

	Decrease	Increase
Convincing:	**Breastfeeding**	**Alcohol**
Probable:	**Adiposity**	**Height**
		Greater Birth weight
Limited (sug):	**Physical Activity**	
Limited (incon):	**Foods and nutrients**	

- **Factors that modify the risk of BC in _post-menopausal_ women**

	Decrease	Increase
Convincing:	**Breastfeeding**	**Alcohol**
		Body fatness
		Height
Probable:	**Physical Activity**	**Abdominal fatness, weight gain**
Limited (sug):		**Total fat**
Limited (incon):	**Foods and nutrients**	

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WCRF/AICR, 2007

Dietary Factors and Breast Cancer

- **High intake of sugar and fast absorbed carbohydrate (jam, sweet drinks, doughnuts)**

- **Low intake of fiber (in particular vegtable fiber)**

- **Low intake of folate (green leafy vegetables (spinach, asparagus) lentil, garbanzo beans, and fortified cereals)**

- **High levels of trans-fatty acids (processed food)**

- **High alcohol intake (pattern of drinking and age start drinking)**

- **Adolescent diet (meat and fat intake)**

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Romieu I, 2012

Dietary Fiber, GL, GI, CHO and Breast Cancer

Dietary Fiber

GI, GL, CHO

Ferrari et al, AJCN 2013; Romieu et al AJCN 2012

Dietary Fiber and CHO variables expressed as g/day

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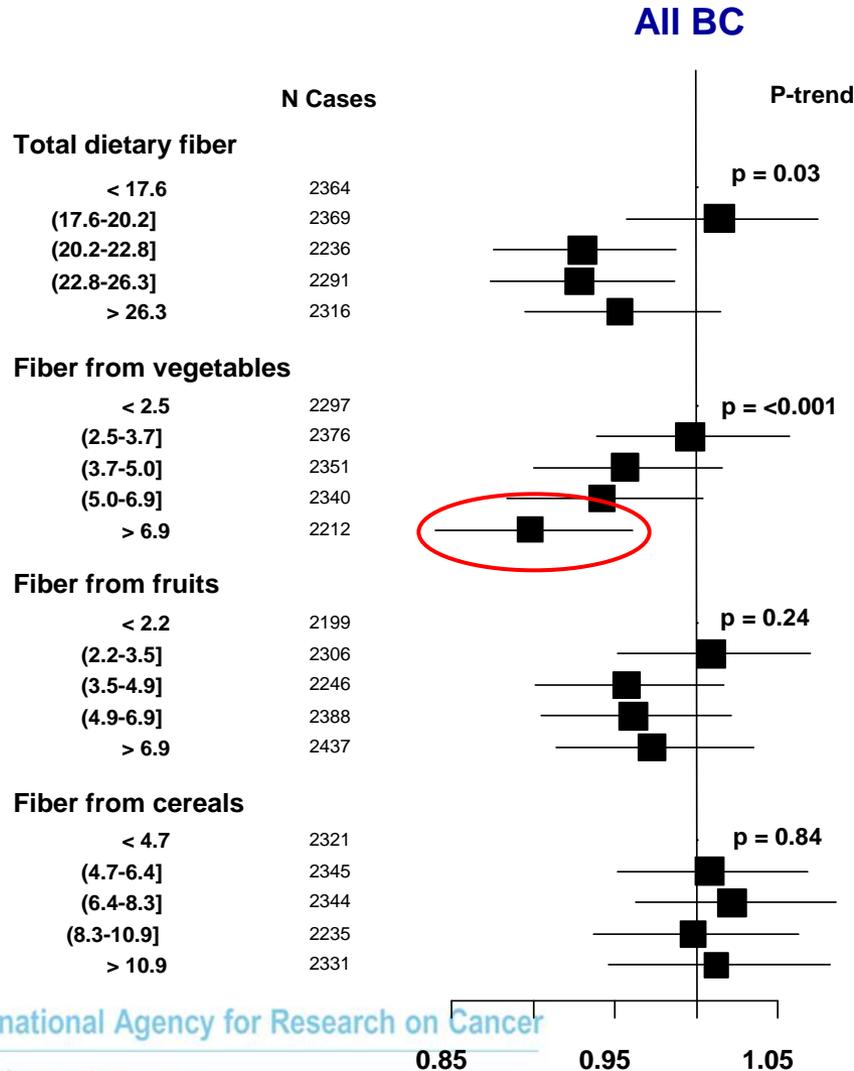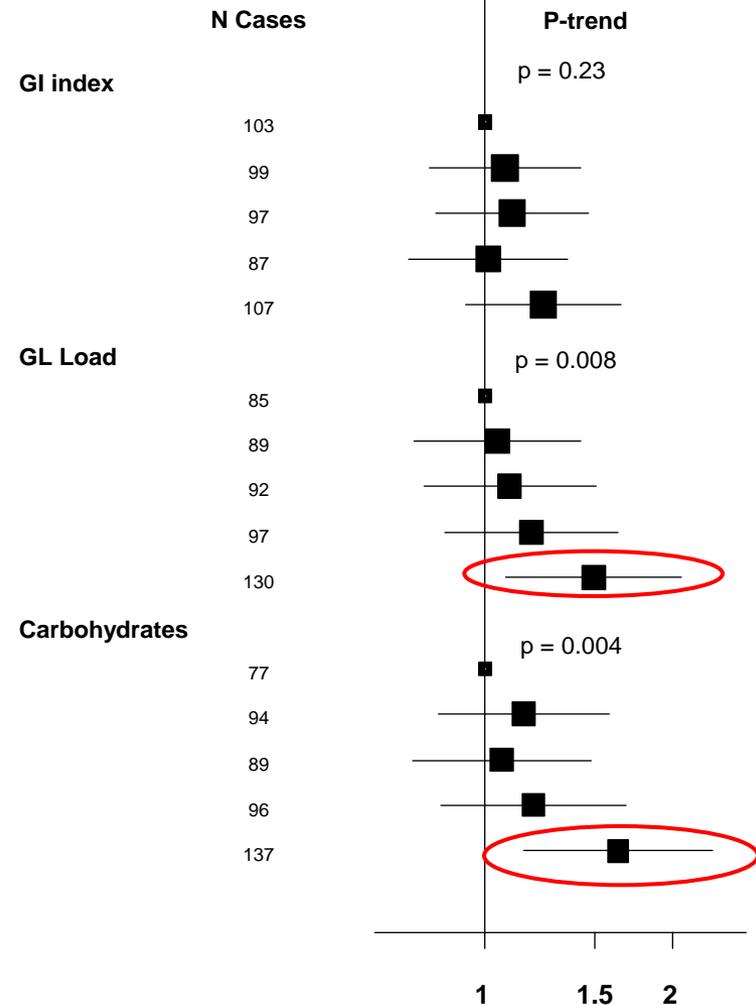
Trans Fatty Acids and Breast Cancer E3N-EPIC

Chajès et al, Am J Epidemiol 2008
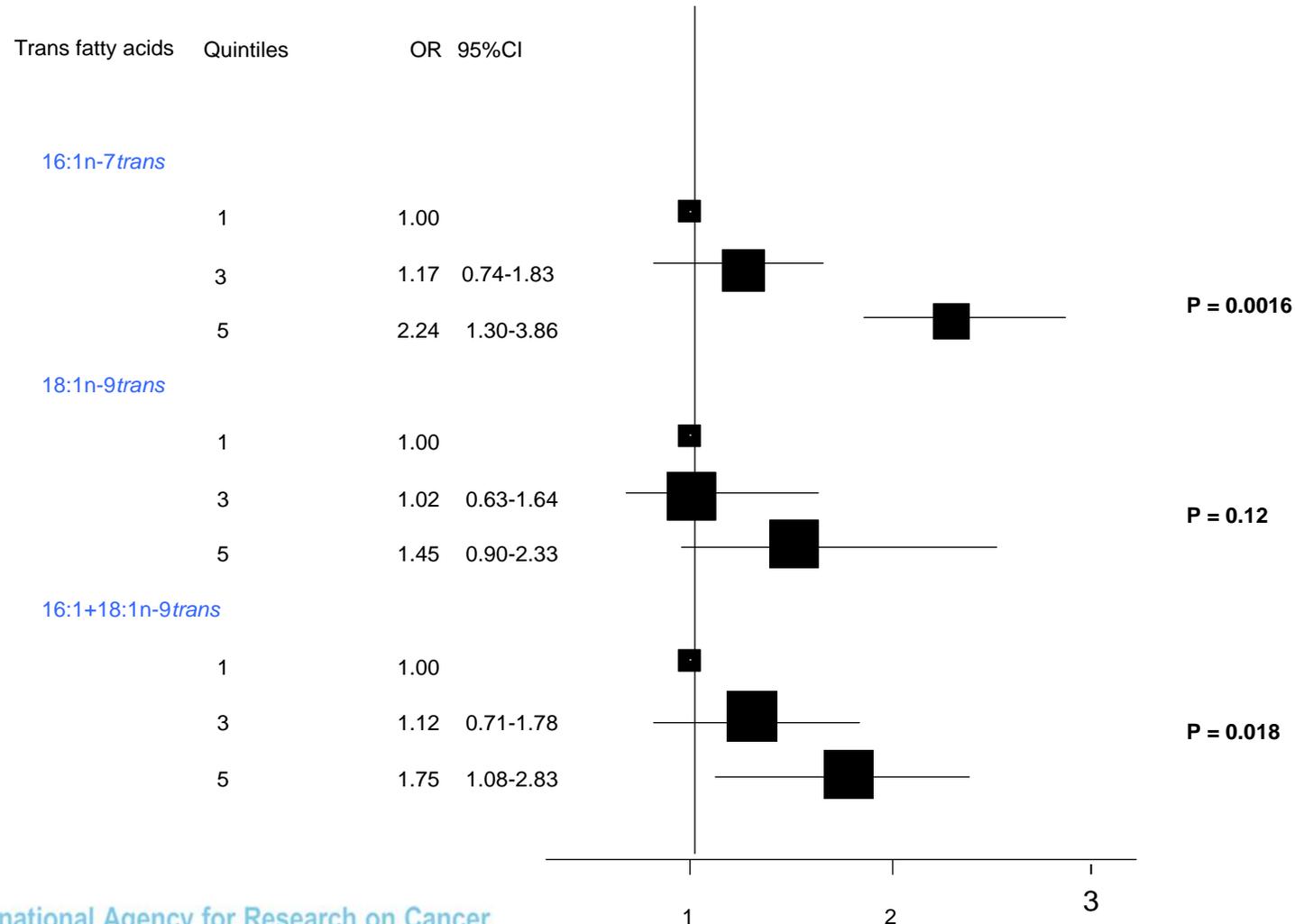
Dietary Pattern and Breast Cancer

Meta-analysis of studies on Dietary Pattern and BC

Most studies identify 2 or 3 dietary patterns:
- **Prudent/healthy (n=18)**
- **Western/unhealthy (n=17)**
- **Drinker (n=4)**

Prudent pattern: OR $_{highest/lowest}$= 12% (1%-23% p=0.02)
Rich in fruits, vegetables, chicken, fish, low fat dairy products and fiber

Drinker pattern: OR $_{highest/lowest}$ = 21% (4%-41% p=0.01)
High consumption of wine, beer ans spirits

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Life Style and Breast Cancer

- **WCRF life style recommendations:**
  - Be physically active as part of everyday life
  - Limit consumption of energy-dense food ; avoid sugary drinks
  - East mostly foods of plant origin (fruits and vegetables, fiber)
  - Limit intake of red meat and avoid processed meat
  - Limit alcohol drinks
  - Breastfeed at least 6 month

- **Index**

  All women: $OR_{Q4-Q1} = 0.55$ (0.40-0.75, $p_{trend} < 0.01$),

  Premenopause: $OR_{Q4-Q1} = 0.47$ (0.29-0.77, $p_{trend} = 0.06$)

  Postmenopausal: $OR_{Q4-Q1} = 0.60$ (0.39-0.92, $p_{trend} < 0.01$)

Fanidi A et al (submitted)

Vitamin D and Breast Cancer

Vitamin D has been shown to favourably affect several mechanisms of cancer development:

- Decrease: cell proliferation, inflammation, oxidative stress, angiogenesis
- Increase: cell differentiation, apoptosis, immunosurveillance
- Low levels in Mexican women (36% <20ng/ml and 9%>30ng/ml in CAMA controls)

Breast Cancer Risk among Mexican women:
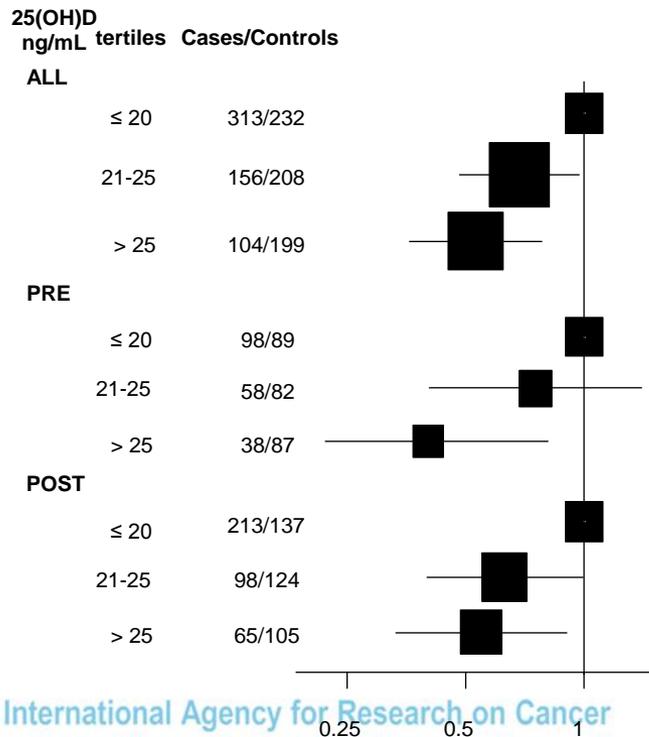
25(OH)D ng/mL tertiles	Cases/Controls
ALL	
≤ 20	313/232
21-25	156/208
> 25	104/199
PRE	
≤ 20	98/89
21-25	58/82
> 25	38/87
POST	
≤ 20	213/137
21-25	98/124
> 25	65/105

0.25   0.5   1

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Original paper

Serum 25-hydroxyvitamin D and risk of breast cancer: results of a large population-based case–control study in Mexican women

Veronika Fedirko [1], Gabriela Torres-Mejía [2], Carolina Ortega-Olvera [2], Carine Biessy [1], Angelica Angeles-Llerenas [2], Eduardo Lazcano-Ponce [2], Vicente A. Saldaña-Quiroz [3] and Isabelle Romieu [1,2]

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(2) Centro de Investigaciones en Salud Poblacional, National Institute of Public Health/Instituto Nacional de Salud Pública, Av. Universidad No. 655, Col. Sta. Ma. Ahucatitlán, Cuernavaca Morelos, CP, 62100, México

(3) Hospital de Gineco-Pediatría No. 71 "Lic. Benito Coquet Lagunes", Instituto Mexicano del Seg (IMSS), Avenida Díaz Mirón s/n, esq. Cedros, Fracc. Floresta, Veracruz, CP, 91920, México

Isabelle Romieu
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Adult weight gain and Breast Cancer by ER⁺

First author, year (no. of cases / study size or controls)   RE (95% CI)

Cohort studies, ER+PR+
Feigelson, 2006 (445 / 44,161) post — 2.42 (1.82 , 3.23)
Ahn, 2007 (202 / 99,039) post — 2.69 (1.74 , 4.17)
Palmer, 2007 (82 / 9,542) post — 1.29 (0.73 , 2.28)

Pooled estimate, cohort ER+PR+ — 2.17 (1.48 , 2.85)

Case-control studies, ER+PR+
Wenten, 2002 (133 / 813) non-Hispanic mixed — 1.05 (0.6 , 1.84)
Wenten, 2002 (133 / 813) Hispanic mixed — 3.04 (1.47 , 6.26)
Enger, 2000 (450 / 1,091) post — 2.32 (1.58 , 3.41)
Eng, 2005 (387 / 1,006) post — 2.17 (1.38 , 3.42)
Rosenberg, 2006 (622 / 3,065) post — 2.7 (1.9 , 3.8)

Pooled estimate, case-control ER+PR+ — 2.25 (1.69 , 2.81)

Case-control studies, ER+
Slattery, 2007 (801 / 1,577) non-Hispanic mixed — 1.13 (0.85 , 1.5)
Slattery, 2007 (379 / 898) Hispanic mixed — 1.17 (0.73 , 1.86)
Han, 2006 (510 / 1,495) post — 2.42 (1.62 , 3.61)

Pooled estimate, case-control ER+ — 1.57 (0.74 , 2.4)

Pooled estimate, all studies — 2.03 (1.62 , 2.45)

Vrieling A et al 2012

Physical Activity and Breast Cancer

Type:
- **Recreational:**   average 21% decrease
- **Occupational:**   average 13% decrease
- **Household:**   average 21% decrease
- **Walking/cycling:** average 18% decrease

Intensity
- **Moderate activity – average 15% risk reduction**
- **Vigorous activity – average 18% risk reduction**

Duration
- **2-3 hours/week – 9%**
- **>6 hours/week – 18%**

Fridenreich C. 2008

Perspective for Prevention

- **Maintaining a healthy weight in adulthood**

- **Moderate intake of alcohol**

- **Limit consumption of energy-dense food ; avoid sugary drinks**

- **East mostly foods of plant origin (fruits and vegetables, fiber)**

- **Regular Physical activity**

- **Potential protective role of soy products, folate and vitamin D**

- **Limit consumption of processed foods**

Breast Cancer- FACTS

- **Most research is conducted in HICs with few data on premenopausal BC**

- **Breast cancer is an heterogeneous disease- with different phenotypes and we do not know the distribution of these phenotypes in LA countries**

- **Risk factors for different phenotypes are likely to be different**

- **Premenopausal cancer appears to be the major threats in LA countries**

- **Knowledge about specific risk factors are needed for evidence-based preventive strategies**

- **Several common risk factors between cancer and other NCDs**

Gaps in Knowledge for Prevention

- **Distribution of BC phenotypes in LA countries**

- **Specific risk factors related to BC phenotypes**

- **Genetic factors –**

    - **tumor sequencing- pathway analyses**
    - **susceptibilty alleles**

- **Role of Environment - gene interaction**

- **Window of susceptibility – Epigenetics**

- **Health system and behavioral research – to define the best strategy to support preventive action and behavioral changes**
- **Strategy to involve all stake holders and develop policy**

Factors that affect the risk of cancer: a conceptual framework

The nine actors: impact of concerted action
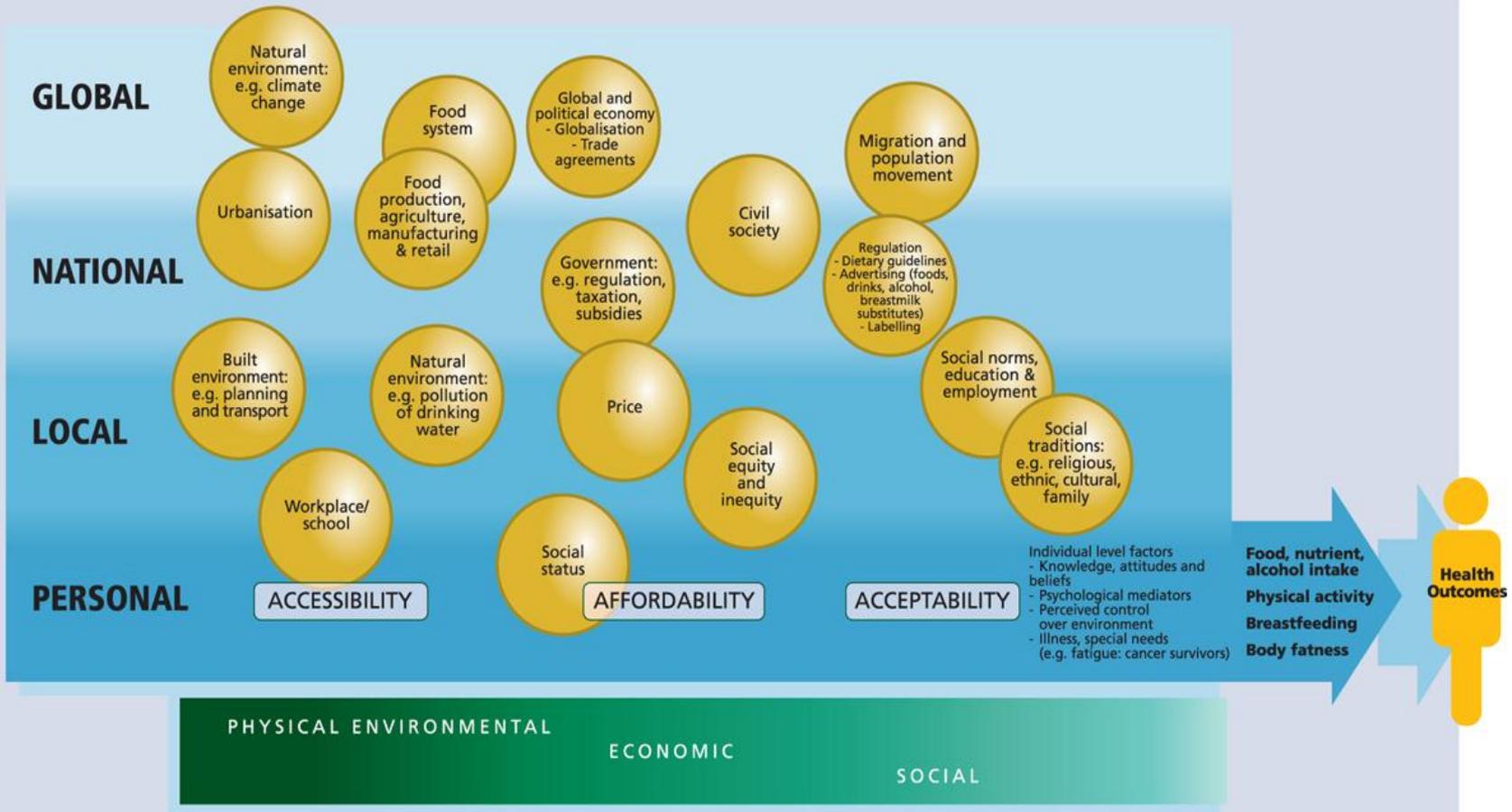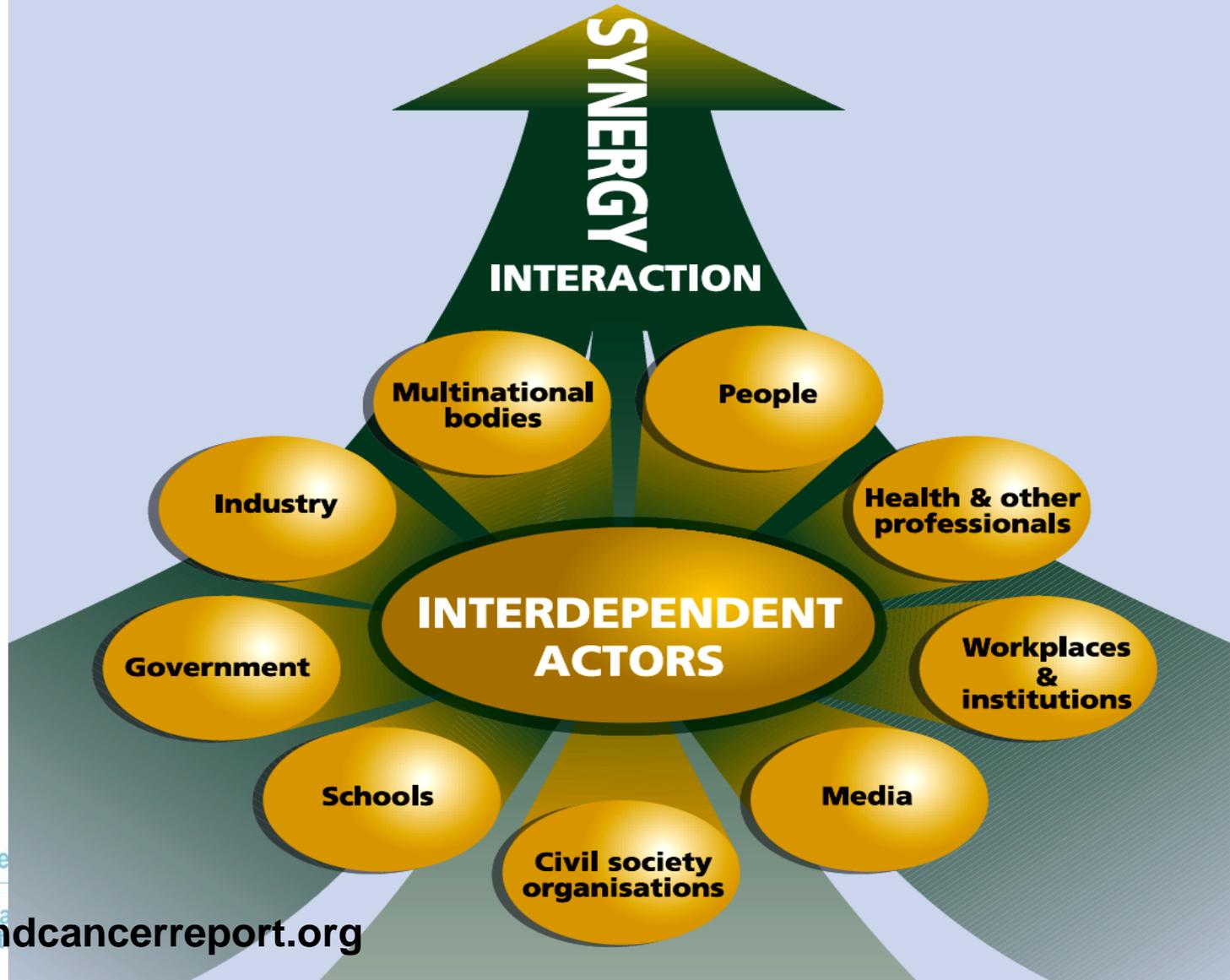
Breast Cancer Etiology
Integrated Approach Towards BC Characterization For Improving Prevention And Treatment
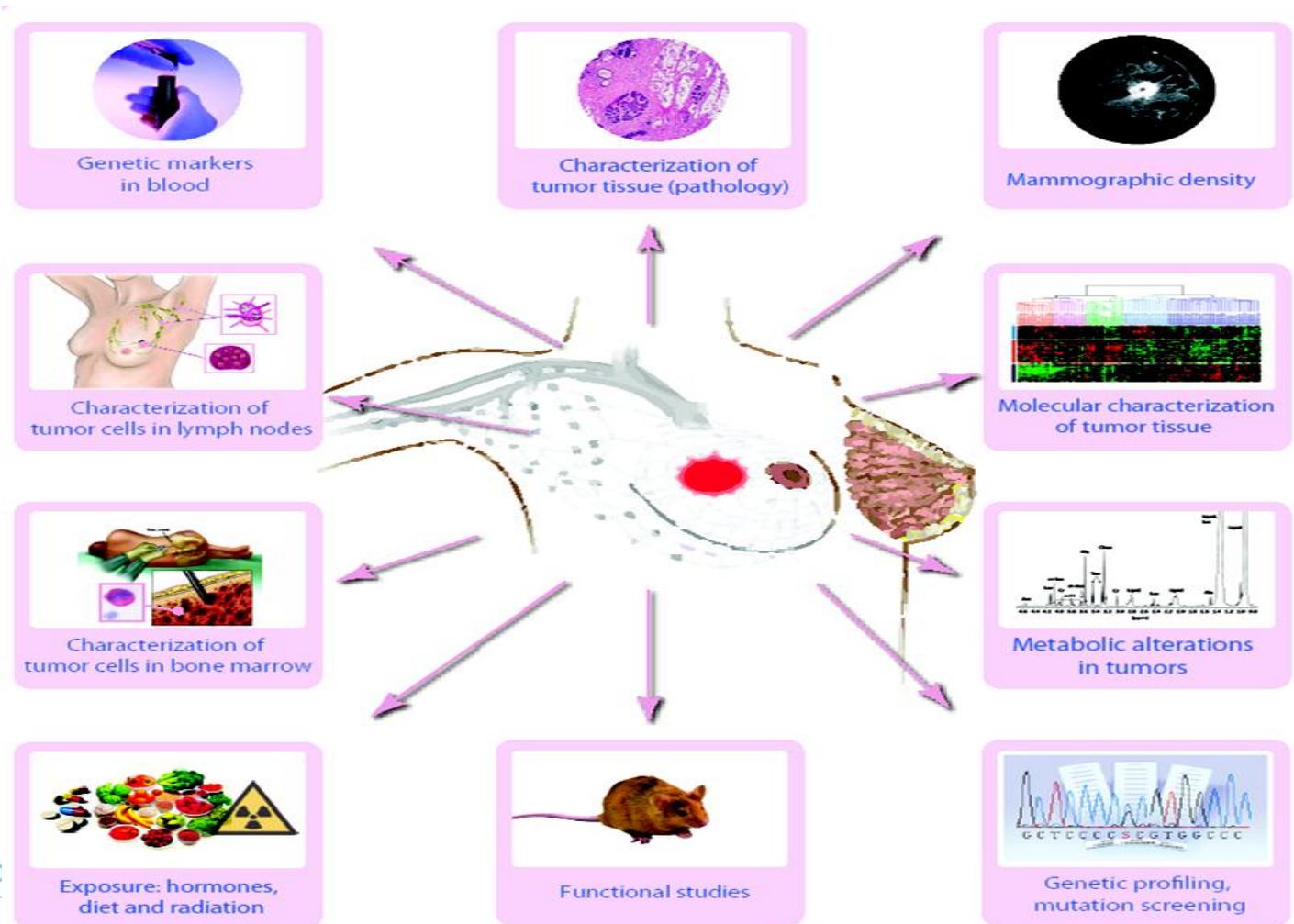
Genetic markers in blood

Characterization of tumor tissue (pathology)

Mammographic density

Characterization of tumor cells in lymph nodes

Molecular characterization of tumor tissue

Characterization of tumor cells in bone marrow

Metabolic alterations in tumors

Exposure: hormones, diet and radiation

Functional studies

Genetic profiling, mutation screening

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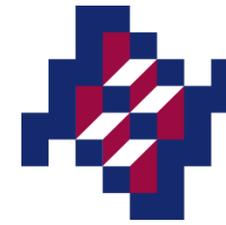
PRECAMA
Molecular Subtypes of Premenopausal Breast Cancer in Latin American Women: A multicenter population based case-control study

IARC- Multicenter study:
Molecular Subtypes of Premenopausal Breast Cancer in Latin American Women

Provide training to Latin American institutions to Improve knowledge of BC phenotypes in Premenopausal LA women and associated risk factors to improve preventive action, early detection and treatment

Feasibility study

- Chile
- Colombia
- Cost Rica
- Mexico

Planned

- Brazil

Objectives and hypothesis

- **Advance the prevention and management of BC in Latin America (LA)** through a better understanding of their molecular, pathological and risk factor patterns

- **Develop a multi-centric case-control study on BC** in centers across LA with structured collection of individual, clinical, pathological information and biological specimens according to **strictly controlled protocols**

- **Characterize the subtypes of premenopausal BC** on the basis of their **molecular and pathological phenotypes**

- **Improve the identification of specific endogenous and exogenous factors** and disentangle the interplay of these different factors with regard to **breast tumor subtypes** and other characteristics.

- **Through these activities, provide advanced training, induce a structuring effect on the BC research community in LA and influence the public health agenda** regarding the management of BC.

PRECAMA Study

- **Standardized protocol** for clinical and exposure data (reproductive history, lifestyle, anthropometry, diet, environment) biological specimens, and tumor sampling and analyses

- **Recruitment** of 500 cases/500 controls per centers (expected 2000 cases/ 2000 controls)

- **Molecular subtypes of premenopausal BC (FHCRC and MAC, IARC)**
    - Classification into Luminal A, Luminal B, Basal like, HER2+/ER- based on IHC biomarkers (ER,PR, HER2, EGFR,CK5/6, Ki67)
    - Analyses of tumor DNA for TP53 mutations (classification into non mutated (WT) and mutated subtypes)

- **Identification of specific endogenous risk factors for specific subtypes of BC**
    - DNA extraction from lymphocytes to assess population admixture (AIMS), mutations in BC susceptibility genes (BRCA1, BRCA2,TP53) and specific SNPs

# Advanced Molecular Analysis of Clinical Tumor Sample For BC Subtyping

- **Advanced molecular analysis of tumor tissues, such as exome sequencing and mRNA or miRNA profiling, have revealed different BC subtypes of clinical significance**

- **Clinical tumor samples, such as formalin-fixed paraffin-embedded (FFPE) tissues can be used for these advanced molecular analysis, allowing for the subtyping of BC in various populations**

- **Analyzing the association between molecular signatures and life-style, environmental, reproductive, or genetic factors in selected populations will help understanding the etiology of BC subtypes and may identify new drug targets**

Genomic landscape in TNBC from Mexico (INCAN)

Human genome

Repetitive

60%

12%

Unannotated
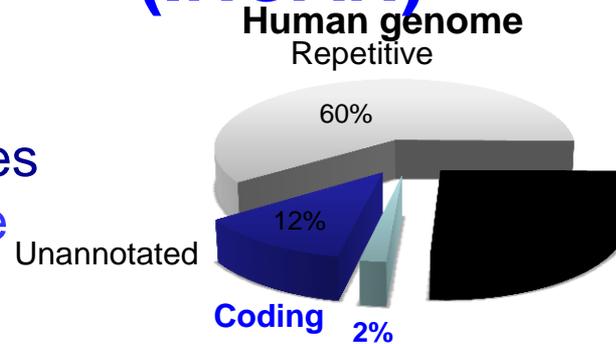
Coding 2%

- Human genome 3 billion bases
- Coding sequence 2%: Exome
- 166,000 Exons

FFPE

DNA → Exome sequencing Copy Number Variations (CNV) → Somatic mutations in coding regions → Pathway analysis

RNA → miRNA mRNA expression → Expression regulation
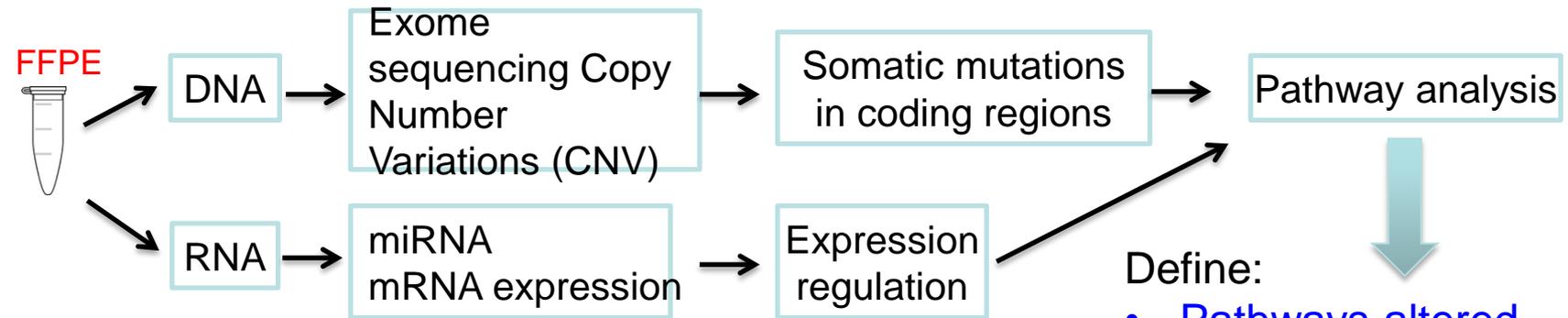
Define:
- Pathways altered
- Tumor molecular phenotypes
- New targets for therapy
- New markers of etiology

Blood

DNA → Exome sequencing → Germline mutations SNPs
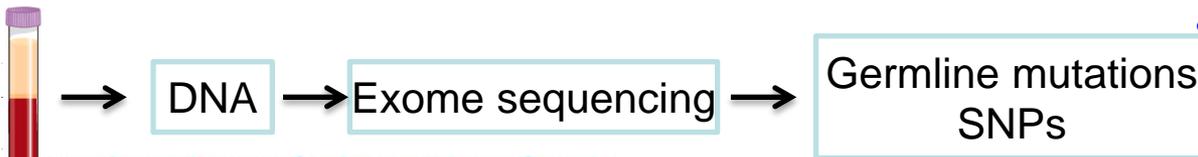
Conclusion

- **The immediate benefits of this study include identifying the major BC phenotypes and acquiring a better understanding of the current clinical context for detection of suspectible subgroups, early detection and diagnosis in young Hispanic women.**

- **This study will increase the capability of LA countries to participate and form partnerships in cancer research, as well as to disseminate information targeted to young Hispanic women about BC awareness and early detection building on existing training and research program**

- **In the future, this feasibility study will be extended and include other centers to develop predictive models for different BC subtypes.**

World Health Organization

An integrated approach for an healthy life style!

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