Acuerdo de cooperación para crear un Laboratorio Asociado Internacional

ENTRE:

El **Institut National de la Santé et de la Recherche Médicale** (el Instituto Nacional de la Salud y de la Investigación Médica), institución pública con fines científicos y tecnológicos, con sede en el 101 de la rue de Tolbiac, 75013 París, Francia, representada por su Director General, el Prof. André Syrota, al que de aquí en adelante se hará referencia como "**INSERM**".

La **Université Paris-Sud 11,** universidad pública con fines científicos y educativos, con sede en Le Château, 91405 Orsay, Francia, representada por su Presidenta, ~~la~~ Prof~~a~~. ~~Anita Bersellini~~, Guy Couarraze a la que de aquí en adelante se hará referencia como "**Paris 11**".

INSERM y **Paris 11** actuando en nombre y representación de INSERM-Paris 11 ERI 20, dirigido por la Dra. Françoise Clavel-Chapelon.

Y:

El **Instituto Nacional de Salud Pública (INSP)**, con sede en la Ciudad de Cuernavaca, Morelos, México, representado por su Director General, el Dr. Mario Henry Rodríguez López, al que de aquí en adelante se hará referencia como "**INSP**".

A las que de aquí en adelante se hará referencia colectivamente como las "**Partes**" e individualmente como la "Parte".

Se acordó lo siguiente:

Antecedentes

El objeto de este acuerdo es definir los términos y las condiciones bajo las cuales cooperarán las Partes, con vistas a ampliar y consolidar las relaciones de naturaleza científica, pero en las que se incluye un elemento de docencia, a fin de contribuir a la investigación biomédica en el campo de "Nutrición, Hormonas y las Enfermedades Crónicas en las Mujeres". Este acuerdo se sustenta en la importancia que reviste este campo científico, así como en la complementariedad científica de las Partes.

El Laboratorio Asociado Internacional es el nombre designado a un laboratorio "virtual" que, en principio, incluye a dos laboratorios de investigación independientes situados en distintas ubicaciones geográficas y que colaboran en un programa conjunto de investigación.

Artículo 1: Objeto

Las Partes tienen el mismo objeto común y, habiendo considerado los beneficios derivados de la coordinación de sus programas de investigación, desean garantizar intercambios efectivos de conocimiento entre ambas.

Con esto en mente, las Partes acordaron cooperar en un programa conjunto de investigación (cuyo contenido está establecido en el Artículo 3), a fin de alcanzar los siguientes objetivos complementarios:

CC

- Promover el desarrollo de la investigación biomédica en el campo de la Nutrición, Hormonas y las Enfermedades Crónicas en las Mujeres;
- Promover los intercambios entre sus institutos: investigadores, becarios de postdoctorado y, posiblemente, miembros del personal técnico;
- Promover intercambios entre los estudiantes.

Las partes tomarán todas las medidas necesarias para garantizar el éxito de la mencionada colaboración, así como para alcanzar estos objetivos, y realizarán consultas a fin de evaluar los logros en curso del programa conjunto de investigación, así como para decidir acerca de las futuras orientaciones y si es o no necesario llevar a cabo medidas correctivas.

Las respectivas contribuciones del programa conjunto de investigación, así como de las Partes, con respecto a las actividades en cuestión, quedarán establecidas respectivamente en los apéndices A y B de este acuerdo.

Artículo 2: Nombre corporativo y domiciliación

El trabajo de investigación se realizará en un laboratorio asociado internacional denominado "INSERM-INSP" (Al que de aquí en adelante se hará referencia como "INSERM-INSP"), que consiste de dos laboratorios independientes situados en Francia y en México respectivamente y que más adelante se describen en el Artículo 3.

Artículo 3: Proyectos y equipos de investigación

Dentro del laboratorio asociado internacional "INSERM-INSP", las Partes han decidido llevar a cabo un programa de investigación conjunta (al que de aquí en adelante se hará referencia como el "Programa") sobre el tema siguiente: "Nutrición, Hormonas y las Enfermedades Crónicas en las Mujeres".

Este Programa se anexa en el Apéndice A, mismo que forma parte integral de este acuerdo.

Los laboratorios siguientes participarán en el Programa y formarán el laboratorio asociado internacional "INSERM-INSP":

- **El Inserm ERI20**, un laboratorio conjunto Inserm-Universidad Paris 11, ubicado en el Instituto Gustave Roussy, 94805 Villejuif, Francia (Laboratorio Inserm-Paris 11), con la Dra. Françoise Clavel-Chapelon como directora del mismo.

- El Grupo CAMA-México, ubicado en el Instituto Nacional de Salud Publica (INSP), con sede en la ciudad de Cuernavaca, México, con la Dra. Isabelle Romieu como directora del mismo.

Al Inserm-Paris 11 y al Grupo CAMA-México de manera conjunta se les denomina los "Laboratorios".

Artículo 4: Recursos suministrados

4.1 Cada una de las partes contribuirá con los recursos (financieros, de personal y de equipo) que se detallan en el B, que forma parte integral del presente acuerdo, y que considere necesarios a la luz de los objetivos de investigación definidos en el mismo.

4.2 Intercambios de material biológico

Se entiende que en el caso en que las Partes intercambien materiales para el desempeño del Programa o, de manera más general, dentro del marco de referencia del presente acuerdo, la Parte que reciba dicho

material (la "Parte Receptora") utilizará los materiales exclusivamente dentro de dicho marco de referencia o, en el caso del Programa, únicamente para el Programa, durante el plazo de este Programa y en el laboratorio donde se desempeñe el Programa y bajo el control del director de la Parte Receptora que se defina para el Programa y no se le dará ningún otro uso (incluyendo, de manera enunciativa y no limitativa a: todo uso comercial o toda administración de los materiales a seres humanos, o el uso del material para propósitos de diagnóstico que involucren a seres humanos en pruebas clínicas o de cualquier otra índole, o para la producción de cualquier producto comercial). Según lo convenido, no se confiere a la Parte Receptora ninguna licencia explícita ni implícita, ni ningún derecho de ninguna naturaleza, fuera del derecho limitado a utilizar los materiales.

En ningún caso deberá la Parte Receptora transferir los materiales a ningún tercero. El acceso a los materiales se limitará a los empleados de la Parte Receptora involucrados en el desempeño del Programa o del propósito para el cual se hayan transferido los materiales. La Parte Receptora deberá proteger a los materiales aplicándoles el mismo grado de seguridad que aplica a su propio material e información confidenciales, pero en ningún caso deberá ser inferior a un grado razonable de seguridad. La Parte Receptora deberá cumplir con todas las leyes supranacionales, nacionales, estatales y locales, con los reglamentos y lineamientos pertinentes al uso de los materiales, incluyendo, de manera enunciativa y no limitativa a: las leyes pertinentes al uso de animales en experimentos y la realización de pruebas, la producción, el almacenaje, la transportación, la importación, la exportación, el empaquetado y el etiquetado de los materiales.

La Parte Receptora descontinuará su uso del material y devolverá el material, al recibir instrucciones justificadas por escrito de hacerlo por parte del proveedor, o destruirá cualquier material restante y certificará dicha destrucción por medio de una notificación por escrito al proveedor.

Toda importación/exportación de material biológico humano se deberá llevar a cabo de acuerdo con las leyes francesas y mexicanas.

Artículo 5: Obligación Legal

Cada una de las Partes deberá, bajo su propia responsabilidad, por su propia obligación legal, y de acuerdo con sus propias reglas, administrar todos los recursos que provea dentro del contexto del presente acuerdo (el equipo, el local, las instalaciones, el personal).

El personal empleado por cualquiera de las Partes y que trabaje para el Laboratorio Asociado Internacional, permanecerá afiliado a su empleador original. Respecto a esto, cada Parte será responsable de proporcionar la cobertura apropiada a sus representantes, de acuerdo con los reglamentos vigentes relativos a la seguridad social y a las lesiones o enfermedades ocupacionales, y asumirá todas las formalidades legales necesarias asociadas a los mismos.

Por lo tanto, la compensación por cualquier daño sufrido por el personal de cualquiera de las partes como resultado del presente acuerdo o a través de la aplicación del mismo, será proporcionado dentro del contexto de la legislación vigente relativa a la seguridad social y a las lesiones o enfermedades ocupacionales y a la luz de la situación del individuo en cuestión.

Cada una de las Partes tendrá la responsabilidad legal, bajo las disposiciones de la legislación civil ordinaria, por cualquier daño o lesión provocada por su personal a la otra Parte o a terceros durante la aplicación del presente acuerdo, incluyendo los daños o lesiones resultantes del uso de los materiales o del equipo puestos a disposición de dicho personal.

Artículo 6: Confidencialidad

6.1 Ambas partes convienen en no comunicar a terceros ningún conocimiento ni información a los cuales tengan acceso dentro del contexto del presente acuerdo, sin el consentimiento por escrito de la otra Parte.

Sin embargo, esta promesa no se aplica a la información siguiente:

- La información que ya sea del dominio público al momento de su comunicación, o que de manera posterior ingrese al dominio público sin que sea a través de ninguna falta o negligencia por parte de la Parte que la reciba;
- La información comunicada a una de las Partes por algún tercero sin ninguna estipulación acerca de su confidencialidad;
- La información que ya se encuentre en poder de la Parte antes de serle comunicada por la otra Parte;
- La información descubierta o desarrollada en forma independiente por una de las Partes sin el uso de información proveniente de la otra Parte;
- La información que deba ser revelada por ley.

6.2 Ninguna de las Partes deberá previamente utilizar el nombre de la otra parte en ninguna publicidad, boletín de prensa, anuncio, o material promocional que involucre al contenido del presente acuerdo, sin el consentimiento previo por escrito de la otra Parte. El Artículo 6.2 permanecerá vigente por lo menos durante un año más a la terminación o rescisión del presente acuerdo.

Artículo 7: Publicación

Los resultados del Programa llevado a cabo en el contexto del Laboratorio Asociados Internacional serán el tema de las publicaciones conjuntas de los dos laboratorios.

Los trabajos relativos a los resultados proporcionarán los nombres de los autores y de las instituciones a las cuales éstos pertenecen, de acuerdo con la práctica acostumbrada.

La Parte que sea propietaria única de los resultados del Programa está en libertad de proceder a la publicación y/o a la comunicación relativa a dichos resultados.

En los demás casos, de manera previa a las publicaciones escritas, orales, o audiovisuales de los resultados en copropiedad por parte de una de las Partes (la "Parte Presentadora"), la Parte Presentadora deberá someter primero a la otra Parte (la "Parte Receptora") un manuscrito de la publicación propuesta, con una anticipación mínima de treinta (30 días) antes de dicha publicación, para su revisión por la Parte Receptora. A menos que la Parte Receptora informe por escrito a la Parte Presentadora durante este periodo de treinta (30) días que la publicación propuesta debe demorarse con el fin de proteger a algún invento patentable, o cambiarse para evitar la revelación de secretos comerciales o conocimientos prácticos (know-how) confidenciales, la Parte Presentadora tendrá la libertad de publicar dichos resultados sin restricción. En caso de que sea necesaria una demora de la publicación propuesta, por alguna razón razonable, la Parte Presentadora deberá retener dicha presentación de la publicación por un periodo adicional acordado de buena fe por las Partes; dicha postergación no excederá el plazo de seis (6) meses, contados a partir de que la Parte Presentadora reciba dicho aviso.

El documento relativo a los resultados dará el nombre del laboratorio asociado internacional, los nombres de los autores y de las instituciones a las cuales pertenecen, de acuerdo con la práctica acostumbrada y de conformidad con el documento sobre direcciones y afiliaciones bibliométricas del Inserm (así en el original: **Inserm Charte bibliometric addresses and affiliations**):
http://www.eva.inserm.fr/Bibliometrie/Visibilite/Modeles_adresses_4eme%20version_2-04-07.pdf

Artículo 8: Propiedad Intelectual y evaluación de los resultados

8.1 Cada una de las partes es y sigue siendo la única propietaria de los derechos de propiedad intelectual e industrial poseídos o controlados por cada Parte de manera previa a este acuerdo y/o adquiridos en paralelo al mismo.

8.2 Las Partes reconocen su interés común por obtener una protección válida de su propiedad intelectual y por proteger sus intereses comerciales. Para propósitos del presente acuerdo, la palabra "invento" incluye cualquier invento, descubrimiento, obra de autoría, software, información o dato, patentable o no patentable, que sea concebido, desarrollado, o reducido a la práctica durante el curso del Programa.

Los inventos hechos exclusivamente por los inventores de una de las Partes ("Invento Exclusivo") serán propiedad de dicha Parte de acuerdo con su política sobre la propiedad de los inventos. Los inventos hechos de manera conjunta por varios inventores de las Partes serán propiedad conjunta ("Invento Conjunto"). La propiedad del invento será determinada de acuerdo con los principios de las leyes sobre patentes.

8.3 Ninguna de las Partes deberá hacer ninguna reclamación sobre el Invento Exclusivo de la otra Parte ni tendrá ningún derecho a ser compensada en conexión con ninguna licencia otorgada por la otra Parte.

8.4 Las Partes convienen consultar una con la otra, de buena fe, todas las cuestiones relacionadas con la solicitud, la tramitación, el mantenimiento y la explotación del Invento Conjunto.

Sobre la base de caso por caso, las Partes acordarán designar a una de ellas para que asuma la responsabilidad principal relativa a la protección de la patente y de la licencia del Invento Conjunto, con la completa asistencia y cooperación de las otras Partes. Las partes convienen en designar a la parte que tenga el mayor conocimiento y experiencia sobre el contenido del Invento Conjunto.

Cada una de las Partes consultará con la otra los asuntos importantes relacionados con la protección y el otorgamiento de licencias por las cuales sea responsable, la mantendrá informada sobre dichos asuntos, y deberá proporcionar a las otras Partes copias de todos los documentos relevantes.

Las Partes pueden acordar concluir un acuerdo de copropiedad que precise la participación de todos los gastos e ingresos relativos al invento, de acuerdo con su contribución respectiva al Invento Conjunto.

Ninguna de las Partes puede ni otorgar una licencia, ni asignar su interés en un Invento Conjunto, a ningún tercero sin el consentimiento previo por escrito de las demás Partes.

Cada una de las Partes puede utilizar el Invento Conjunto con fines de investigación y educativos.

8.5 Cada Parte será responsable de compensar a aquellos inventores considerados miembros de su personal al momento de la invención, de acuerdo con sus propias políticas y códigos de práctica para otorgar dicha compensación.

Artículo 9: Contrato con terceros

Los términos y las condiciones de la colaboración con terceros serán definidos entre las Partes y estarán sujetos a un acuerdo específico que se pacte con los terceros antes mencionados.

Dentro del marco de las actividades de investigación en común, una parte podría utilizar a algún subcontratista (un tercero conforme al presente) con el fin de realizar uno o más servicios necesarios para el logro del proyecto de investigación. Solamente la Parte subcontratante mantendrá la responsabilidad por la buena ejecución, por parte del subcontratista, de las tares que se le encomienden y se asegurará que el subcontratista respete los términos del presente acuerdo, en particular aquellos relacionados con la confidencialidad (Artículo 6) y con la propiedad intelectual (Artículo 8).

Artículo 10: Plazo y fecha de entrada en vigor del Acuerdo

Este acuerdo se celebra por un plazo de cuatro (4) años y entrará en vigor en la fecha en que se firme. Seis (6) meses antes de la fecha de su vencimiento, las Partes se reunirán para decidir si este acuerdo se renueva o no y, en caso afirmativo, bajo cuáles términos. La renovación del acuerdo se deberá formalizar en un nuevo documento escrito, o por medio de una enmienda al presente acuerdo.

Artículo 11: Cancelación

Este acuerdo puede ser rescindido por cualquiera de las Partes por medio de la notificación por escrito, particularmente si la otra Parte falla en el cumplimiento de cualquiera de sus deberes o responsabilidades, o incumple cualquiera de sus obligaciones bajo el presente acuerdo y si dicha falla o incumplimiento no queda subsanada dentro de los sesenta (60) días posteriores al recibo de la notificación por escrito.

En particular, las Partes pueden cancelar este acuerdo:

- En caso de cambios sustanciales a los recursos adjudicados al Laboratorio Asociado Internacional.

- En caso de incumplimiento de las disposiciones del presente acuerdo, en particular lo que concierne al uso de cualquier fondo proporcionado para los propósitos relacionados a los fines de este instrumento.

Si alguna de las Partes llega a cancelar el acuerdo de esta manera, se efectuará una reunión entre las Partes para discutir todas las consecuencias, en especial las consecuencias de índole financiera.

Artículo 12: Supervivencia

Las disposiciones de los artículos 6, 7, 8, 8 y 14 sobrevivirán a la caducidad o a la rescisión del presente Acuerdo, o a la retractación del mismo.

Artículo 13: Disposiciones Varias

Este acuerdo y los apéndices del mismo representan las intenciones completas de las Partes relativas al objeto del mismo. Si cualquiera de las disposiciones se vuelve nula y sin efecto, o inaplicable, los demás términos y condiciones del acuerdo no se verán afectados y permanecerán siendo válidos y aplicables.
En caso de cualquier modificación a este acuerdo, se deberá de realizar un adendum por escrito, que se establecerá siguiendo los lineamientos pactados en este instrumento.

Artículo 14: Disputas

Si surge cualquier disputa entre las Partes respecto a la interpretación o a la aplicación del presente acuerdo, éstas aceptarán someter el asunto a mediadores antes de llevarlo ante los tribunales. Cada parte designará a un mediador, a menos que ambas Partes puedan convenir en elegir a un solo mediador. Los mediadores harán su mejor esfuerzo por resolver todas las dificultades y encontrar una solución amistosa que resulte aceptable para ambas Partes, dentro de un plazo de sesenta (60) días contados a partir de la fecha de su nombramiento.

Si no es posible alcanzar un acuerdo, la disputa se llevará ante los tribunales competentes, según hayan sido designados por las partes o, si no se puede llegar a ningún acuerdo sobre este punto, por los mediadores.

En 3 ejemplares originales.

En París y México.

Pr André Syrota
Directeur Général
INSERM

Date : 03/04/09

Pr Guy ~~Coarraze~~ Couraze
Président
Paris 11

Date : 7 mai 2009

Mario Henry Rodriguez, MD-PhD
Directeur Général
INSP

Date : _____

INSTITUTO NACIONAL DE SALUD PÚBLICA
ASUNTOS JURIDICOS
REGISTRO DE CONTRATOS
No. 042
FECHA: 27-01-09 RUBRICA:

Appendix A

JOINT RESEARCH PROGRAM

International Associated Laboratory in Nutrition, Hormones and Chronic Diseases in women

ABSTRACT

International Associated Laboratory: Nutrition, hormones and chronic diseases in women

The purpose of the present project is to develop a collaboration between groups with long-term international expertise in the field of chronic diseases epidemiology in the context of the construction of an *International Associated Laboratory*. The proposal is based on two departments from two institutions, one in Mexico and one in France who share the same interest in nutrition, hormones and chronic diseases, in particular breast cancer (BC) and type II diabetes, both related to obesity. Both groups have major research interest in environment, biology and genetics and in understanding risk factors for chronic diseases in women using analytical epidemiological research. The association will provide a sustainable structure for the teams already involved in numerous national and international networks, which will increase the understanding of these diseases which incidence is growing in both countries The two counterparts have developed scientific collaboration for many years. They have complementary expertise, background and common interest in chronic diseases epidemiology.

Lines of research as final targets for collaborations are as follows:

- To investigate the associations between major chronic diseases (with special interest for BC and type II diabetes) and metabolic factors, diet, physical activity, use of hormonal treatments, reproductive factors, and early life exposure to environmental factors (nutrition, life style..)
- To assess the relationship between chronic diseases and serum biological markers (nutrition, hormones, inflammation ...)
- To analyze the interaction between genetic characteristics and these potential risk factors.

Collaborative research will rely mainly on two large cohort studies, the on-going E3N cohort in France, and the recently initiated EsMaestras cohort study in Mexico.

The construction of this International Associated Laboratory will include core teams of both institutions and support scientific exchange, technology transfer and human resource development in a priority area for both Mexico and France.

A coordinating team integrated by a person from each institution (F. Clavel-Chapelon for INSERM, and I. Romieu for INSP) is the basis of the organisational structure. Regular visits and exchanges of senior and junior scientists are planned, during which seminars, scientific interaction and development of scientific manuscripts will be performed. In addition,

innovative research in priority areas will be developed.
This scientific collaboration will improve the competitiveness of both institutions in the field of chronic diseases research and therefore will support the development of preventive measures on the major public health issues. This project has received full support from the Mexican government, and is in line with INSERM priorities to expand international collaboration and facilitate exchange of junior and senior researchers within a common research framework.

1. PARTICIPANT GROUPS

The association concerns groups working on chronic diseases epidemiology in women from two institutions: **the ERI 20 INSERM in France and INSP in Mexico**. The main participants from each group are listed below :

ERI 20 INSERM, Villejuif, France
Françoise Clavel-Chapelon, PhD, Research Director (Dr2) (Team Leader)
Marie Christine Boutron-Ruault, MD, PhD, Research Director (Dr2)
Véronique Chajès, PhD
Agnès Fournier, MSc, PhD
Alban Fabre, MPH
Pierre Engel, Pharmacist, MPH
Blandine Guillain de Lauzon, PHD
Aline Charles, MD, PHD

INSP, Cuernavaca, Mexico
Isabelle Romieu, MD, MPH, ScD (Team Leader)
Eduardo Lazcano, MD, PhD Director CISP
Juan Rivera PhD, Director CYND
Ruy López, MD, PhD
Gabriela Torres, MD, PhD
Luisa Sanchez PhD
Martin Lajous, MD, MPH
Angélica Angeles, MD, MSc

2. OBJECTIVES AND CONTEXT

2.1 Rationale

Epidemiologic and mechanistic data suggest that risk factors for major chronic diseases act both early in life and soon before diagnosis(1, 2). Dietary and lifestyle factors have been hypothesized as determinants of these chronic diseases; still, few have been unequivocally associated. One key risk factor appears to be **obesity** and adult weight gain, which affects both steroid hormones (e.g. estrogen) and growth factors (e.g. insulin) metabolic pathways. **Body composition** and **dietary intake** can act at many points in the aetiology and/or development of these diseases throughout life(3, 4), hence studies with repeated exposure assessment, and long prospective follow-up are especially valuable. Of particular interest are **BC** or **Type II diabetes** which are both increasing very rapidly in the Mexican population, and which represent a large part of the burden of chronic diseases in French women. Furthermore, it has been suggested that BC risk may be increased among women with type II diabetes(5).

2.1.1. Chronic diseases in women: Breast cancer and Type II diabetes

Breast cancer in Mexico

The incidence of BC in Mexico is still relatively low as compared to Western countries(6), but Mexico is currently going through an epidemiological transition with an increasing burden of obesity and chronic disease. From *1979 to 1994*, age-standardized mortality for BC almost doubled from 6.4 to 12.2 deaths per 100,000 women(7). and recent data show that this increase has persisted and breast cancer is now the first cancer in Mexican women. In 2005 the mortality for breast cancer has rechead 15.31 per 100,000 women (INEGI,CONAPO). This increase in mortality, while treatment has improved, reflects an increase in incidence linked in part to changes in women's lifestyles. Later age at first pregnancy, decreasing duration of lactation, fewer pregnancies, hormones consumption, less active lifestyles and substitution of traditional dietary habits have probably contributed to this upward trend(7).

Type II diabetes in Mexico

In Mexico, the mortality due to type II diabetes has increased by 62% between 1980 and 1998(8) and the 2000 nutritional survey suggests a prevalence of 8% of type II diabetes (9). This disease has a very high cost which increased by 26% between 2003- and 2005(10). Fourteen percent of the Mexican population has been diagnosed with type II diabetes between 20 and 40 years(11). Obesity is a strong risk factor for type II diabetes and 60% of the current Mexican population is overweight or obese(12). The association of hypertension, hyperglycemia, hypertriglyceridemia, and low level of HDL with +obesity is observed in 27% of the Mexican population(13) who appear to have a genetic susceptibility to type II diabetes , and the prevalence of type II diabetes in Mexicans is almost twice the prevalence in the white US population(14).

Breast cancer in France

Breast cancer incidence has dramatically increased in the last 20 years, from around 20 000 to around 40 000 new cases each year between 1980 and 2000. Breast cancer is the most frequent cancer in France, and represents more than one third of all cancers diagnosed in French women. The number of breast cancer deaths, around 11 000, has remained stable. Age standardized (on the world population) mortality rate was 19.7 in 2000(15).

Type II diabetes in France

In France, it has been estimated that 2.5 million individuals have type II NIDD, corresponding to a prevalence of 3.5 %. Since 1998, NIDD has been declared a national public health priority, with a specific national NIDD plan within the PNNS (national program for nutrition and health). It is estimated that the incidence of NIDD is progressing by 5 to 6 % per year(16, 17).

2.1.2 Risk factors

Energy balance

Excess body fat is associated with many chronic diseases and overall mortality(18). Therefore, energy balance appears to play a crucial role. Regular exercise and avoidance of weight gain during adult life is beneficial to overall health. For women who are already overweight in midlife or later, weight loss is desirable. Consequently, it is important to assess energy intake and expenditure, and body fatness on disease risk in populations studied by our two research groups. Of major interest, the association between adult adiposity and sedentary lifestyle, and BC may be mediated by increased levels of estrogens (synthesized

by adipocytes) or hyper insulinemia (which can act directly or by reducing IGFs binding proteins)(19-23). Childhood fatness might be a marker of risk later in life (by decreasing paradoxically BC risk)(24-32). Therefore, the evaluation of body build in childhood and adolescence (using self-reported body silhouettes) in addition to assessments of body composition in adulthood needs to be performed. PA can affect hormonal levels(19, 23) and increase levels of sex hormone-binding globulin (SHBG), thereby reducing bioavailable estrogens.(33) Increased PA also reduces insulin resistance and hyperinsulinemia(34), hypothesized to be related to BC(20) and a marker for type II diabetes.

Diet

Most studies on diet and chronic diseases have been conducted in industrialized countries. However, the variation in dietary habits within and between these countries is low, which limits their ability to identify dietary risk factors. Many studies restricted to one homogenous population may not have sufficient variation in intake to overcome the random noise introduced by measurement error. For that reason dietary studies taking advantage of the international variation in dietary habits across industrialized and developing countries are more powerful to explore the association between diet and chronic diseases. In addition characterization of disease phenotype (e.g hormone receptor status in BC or genetic status) will allow a better specification of susceptibility to the influence of diet, which may vary according to the tumour type.

Few dietary factors have been associated with BC. This apparent lack of association may be real, or may be due to measurement error exceeding the variation in the diet studied, and to a low heterogeneity of intake. While alcohol intake has been extensively investigated(18, 35, 36), other dietary factors potentially detrimental such as rapidly absorbed carbohydrates or trans fatty acids (markers of manufactured foods), or potentially beneficial, such as vitamin D, folate intake, omega-3 PUFA, or phytoestrogens have not been sufficiently explored yet.

Oral contraceptive and Hormonal therapy

Oral contraceptive use has been related to BC risk in current users(37) and in premenopausal women when used before the first full term pregnancy(38). The use of menopausal hormone therapy (HMT) combining estrogens and progestins also appeared to increase the risk of BC(37, 39). As for the other risk factors previously mentioned, the contrast in terms of type and use of hormonal use between the populations studied by our two research groups vary widely, in particular with regards to HMT, facilitating the evaluation of these factors on disease risk. In particular, while most studies until now have evaluated estrogens associated with medroxyprogesterone acetate (MPA) or 19-Nor-Testosterone derivatives, other combined estrogen-progestagen therapies are used around the world. For instance, in France, about 70% of estrogen has a transdermal/percutaneous route of administration and the progestogens most used are natural micronized progesterone and its isomer, retroprogesterone. In Mexico, most used post menopausal hormone therapy is conjuguated equine estrogen combined with MPA. Oral contraceptive use has been associated with alterations of carbohydrate metabolism. Few studies have analysed HMT in relation to type II diabetes risk; their results are not consistent(40, 41).

Endogenous hormones

Recent data provide strong evidence that plasma hormone levels are related to both pre and postmenopausal BC risk(42, 43). There is still uncertainty on the role of androgen levels with regard to BC. Breast density is one of the strongest predictors of BC risk and has been considered as an intermediate outcome in studies of BC etiology(44). It has been also hypothesized that breast density reflects cumulative exposure to estrogens and is a good surrogate marker for enhanced exogenous hormone exposure(45), with the most

pronounced effect for HMT combining estrogens and progestins(46, 47). Previous studies have also suggested the role of endogenous sex hormones in the development of type 2 diabetes. Sex-dependent relationship may exist for hormone levels, insulin resistance and risk of type II diabetes.

Genetic factors

While variation of exposure between populations is important to increase the power to detect associations with diseases, genetic admixture needs to be considered, as well as specific genetic polymorphisms that might modify the effect of risk factors. Family and twin studies both indicate that genetic susceptibility is an important determinant of many chronic diseases, in particular BC and type II diabetes (48). However few of these genes have been identified for BC(49) and for type II diabetes (50). Similarly, few gene-environmental interactions have been detected(51). While the identification of mutations in BRCA1/2 genes has explained a substantial proportion of early-onset BC, little is known about common genetic variants associated with sporadic disease. Whole genome studies enable analysis of hundreds of thousands of SNPs in order to identify common genetic variants associated with sporadic cases. Collaborative studies are necessary to identify low-penetrance susceptibility variants. Regarding genetic admixture, latino/hispanic populations are known to be of mixed European, Native American and African ancestry. Recently, it has been proposed that there are several different BC diseases according to their histopathology and to the age at presentation. It has been hypothesized that these differences of BC are due, in part, to complex associations between genetic and environmental BC risk factors. The collaboration between the French and the Mexican groups will permit to merge data in order to achieve sufficient sample sizes to detect more modest effects of genes related to pre-and postmenopausal women and provide a better understanding of the role of genetic admixture and its interaction with environmental factors.

Despite long term research in the field of nutrition and hormones and more recent genetic research, the role of these factors in the risk of chronic diseases is still sparse. There is general agreement that these factors probably play an important role; however there is a lack of well designed prospective studies combining epidemiological, biological and genetic information to better understand their role. The ability to have large ranges of exposure and diverse genetic admixture will facilitate characterizing the role of these factors. In order to study interactions, in particular gene-environment interactions, large numbers are a prerequisite and the heterogeneity in results among our two populations, if any, would certainly be a benefit to better understand biological mechanisms.

2.2 Collaboration and complementarities of the research groups

The two counterparts, research groups at Inserm and INSP, have developed scientific collaboration *since* 2002. They have complementary expertise, background, and common interest, and they share the same strategic perspectives regarding the epidemiology of chronic diseases, in particular BC and type II diabetes, two major priorities in industrialized, transition, and developing countries.

These teams are strong players in the field of **global health epidemiology**, through their participation to international studies such as the European Prospective Investigation on Cancer and Nutrition (EPIC), consortium of cohort studies on genetic determinants, consortium on cervical cancer, University of California San Francisco (UCSF), Moffit Center, Florida, Harvard School of Public Health, Boston) and prior collaboration with major research groups in these areas, workshop and symposium organization (in the field of BC, public

health, nutrition, and respiratory diseases).

They have a strong and **internationally recognized expertise** in analytical epidemiology. They combine methodological expertise in environmental issues and in aspects of public health of relevant importance; they are also among the few international research teams that have collected combined epidemiological, biological and genetic data, and have a large experience in study design, statistical analyses, methods development regarding the assessment of the environment, in particular diet, phenotypic characterization of BC and type II diabetes; they also have an experience of sustained collaboration with groups working in the field of genetics. Both teams have large experience in networking at the international level with major research groups conducting cohort studies.

Efficient research depends on **structure, human resources, and projects**. Projects combining two large cohort studies may be a driving force to build up an *International Associated Laboratory.* These two studies play central roles for the two research groups. Moreover, joining studies with similar design is a required step for replication studies, which are of major importance for investigating genetic associations.

These studies, characterized on one hand by their common aims, common study design, and similar questionnaires for the assessment of lifestyle, and on the other hand by specific population characteristics and genetic admixture constitute a unique opportunity to mutually reinforce our ability to disentangle major determinants of chronic diseases. Existing platforms in both institutions represent the technical counterpart to scientific components necessary for successful collaboration. Our collaboration will be reinforced by frequent visits of senior researchers and young investigators between both groups, the development of joint analyses and joint publications as well as common application for national and international funding on inovative research questions.

3. PROPOSAL-AIMS

3.1 Specific aims

The overall aim for building up this *International Associated Laboratory* is to make significant progress in the field of chronic disease epidemiology in women. As this field needs larger research groups and more integrated scientific activities, the purpose is to develop an association between groups of excellence in this field.

This proposal consists in developing a **stable program of collaboration between the ERI 20 Inserm in France and INSP in Mexico**. The collaboration is applied under the figure of an *International Associated Laboratory*.

The specific aims of this International Associated Laboratory in the epidemiology chronic diseases in women are:

- To establish a **stable collaboration** in chronic disease epidemiology in women in order to increase the variability in lifestyle risk factors of interest, specifically energy balance, diet and use of hormonal treatments
- To share data bases for the analysis of inovative research questions
- To **attract and train new researchers** in this major public health area.
- To **share experience and transfer expertise** on the management of large data bases using the experience of the E3N cohort study
- To join efforts to **improve** efficiency and competitiveness of research **in terms of new area of research by sharing capabilities** (e.g. determination of fatty acid , evaluation of breast density, determination of genetic polymorphisms)

3.2 Strategy of collaboration

The proposed strategy of collaboration between the two groups in different countries is based on the following principles:

1) To develop a **collaborative approach** going beyond the usual project by project initiatives. This approach will capitalize on the expertise of each institution to develop a research agenda on priority issues in the field of chronic diseases epidemiology in women. The I nternational nature of the approach will permit to address health issues of importance both for developed and developing countries and support the training and research team development with common interest.

2) To **exchange knowledge** in our respective fields of expertise and provide an integrated multidisciplinary framework. E3N is the major component of EPIC, and EsMaestras has developed close collaboration with the Nurses Health Studies (NHS) at Harvard University (Boston, USA) and at the University of California (UCSF, San Francisco, USA) for genetic aspects. This illustrates the potential for the cohorts of our research groups to join worldwide consortia of cohort studies aimed at identifying the role of environmental factors and genetics of chronic disease etiology.

3) To **develop and maintain** an *International Associated Laboratory* in chronic diseases epidemiology in women insuring long term research in an integrated multidisciplinary approach. The training and involvement of young researchers in this field is necessary for this project to persist beyond the career span of the investigators that launched these projects . This includes the development of common projects on innovative issues and carry out "cutting edge" research involving clinical, environmental, biological and genetic aspects.

4) To **improve the competitiveness** of both institutions in the field of chronic diseases research and therefore support the development of preventive measures on the major public health issues.

4. SCIENTIFIC PROGRAM

4.1 Framework

The framework of the scientific program is based on the existing capacities in both institutions and previous collaboration.

After a detailed analysis of existing activities, two different types of scientific collaboration have been distinguished:

i) Research areas where both institutions have accumulated substantial expertise and background and are of **common interest** for the future (body composition, diet, physical activity, hormone menopause therapy)

ii) Research areas where the two institutions have complementary expertise, which can result in **added value** to one or both institutions (breast density, biomarkers of nutrient intake, genetics) and areas in which current development is still limited but with **great potential** (gene environment interactions, proteomics, new biological markers)

4.2 Interest of combining cohort studies

Recent laboratory and molecular epidemiology studies have indicated that body size and obesity may be associated with chronic diseases through metabolic pathways (insulin, IGF, estrogen, and their respective receptors). For example high body mass index has been associated with a higher risk of BC in post menopausal women. There is a high prevalence of obesity as well as type II diabetes among Mexican women, and type II diabetes occurs in Mexico at a much younger age than among the white French population. The association between type II diabetes and cancer has been described since long(5). However

mechanisms explaining this association are still not perfectly understood.

Collaboration between our two research teams will enlarge the range of exposure (age, weight, dietary or hormone intake and lifestyle factors) and of genetic characteristics of our two populations. It will enhance our ability to detect relevant epidemiological and genetic associations. It will also increase the statistical power to evaluate the risk in specific subgroups with small number of cases for example in estrogen receptor negative breast tumors.

The existence of a relationship between nutrition and cancer has been repeatedly suggested by experimental, ecological and epidemiological studies, and it is now well acknowledged that nutrition and lifestyle can account for manifold variations in cancer incidence. Endogenous hormones, mainly through the analysis of reproductive factors, have been extensively studied and use of exogenous hormones such as contraceptive pills, hormone menopause therapies or treatments for infertility have been shown to alter the risk of certain cancers in women.

Until the early 90s, the vast majority of the literature on diet or hormone use and cancer derived from case-control studies, although cohort studies on healthy participants were considered preferable, the prospective design allowing i) to avoid numerous biases issuing from a retrospective record, and ii) to collect biological samples, making it possible to improve substantially our understanding of the disease through measurements of various biomarkers.

In an attempt to overcome the limitations of the traditional case-control design, the Inserm-ERI20 set up in 1990 the E3N, the largest epidemiological study ever initiated in France on 100,000 female volunteers, with the aim of producing a large mass of data relevant for the identification of environmental causes of cancer and other chronic diseases in women, in order to contribute to the development of effective public health strategies against cancer and the major chronic diseases. The Inserm-ERI20 group works exclusively on the management and analysis of the E3N cohort study, a study which makes it possible to explore interactions between nutritional, genetic, hormonal, and lifestyle factors.

In Mexico, a similar cohort study of female teachers aged 35 years and older has been started, with the objective of including 100,000 subjects contacted through the Ministry of Education. At present, a baseline questionnaire has been obtained on 40,000 women from two states in Mexico. The participation rate exceeds 70% of the subjects invited to participate.

The scientific program of the **International Associated Laboratory on "Nutrition, hormones and chronic diseases in women"** that we want to set up relies on the parallel analysis of two datasets, which main characteristics are as follows.

4.2.1 General characteristics of the E3N cohort study

The E3N cohort comprises 100,000 female volunteers, aged 40-65 years at baseline in 1990, insured by the Mutuelle Générale de l'Education Nationale (M.G.E.N.), a national Health Insurance Plan, covering mostly teachers. Participants are asked to complete self-administered questionnaires every 24 months on diet, use of hormonal treatments, reproductive factors, anthropometric characteristics and a variety of lifestyle habits (smoking, physical activity, etc.). Each follow-up questionnaire (available at www.E3N.net) investigates

the health status of the participants, including occurrence of cancer. All diagnosed cancers are validated after review of the pathology report obtained from the medical practitioner. In addition, a bank of biological material has been set up, and is available for genetic, metabolic, biochemical and epidemiological investigations of cancer causes and mechanisms

In 1993 E3N became the French part of the European Prospective Investigation on Cancer (EPIC), a collaborative study of over 500,000 subjects in 10 countries, coordinated at the International Agency for Research on Cancer (Lyon).

Epidemiological data
Eight questionnaires have been sent up to now. All recorded information has been computerised and checked. The longitudinal data (same question repeated for updating: on menopause or smoking for instance) are homogeneous. Several validation studies have been performed, revealing very satisfactory results. The rate of lost to follow-up is very low (<6%), due to the opportunity to trace non respondents by the means of the MGEN files through the routine reporting of expenses to be covered when hospitalisation occurs. Pathology reports of cancer cases are routinely requested from the participants' medical doctors and are coded; around 90% of all cancer cases have been histologicaly confirmed.

Biological data
Blood samples have been collected between 1994 and 1998. The participation rate among women invited to participate was about 40%, leading to an approximate number of 25,000 blood drawings, which have been separated into 28 aliquots (plasma, serum, leukocytes, erythrocytes). Plastic straws are used for storage of 28 biological samples per subject, and stored in liquid nitrogen containers (-196°C). The bio-repositories are located at IARC (Lyon) and at the Etablissement Français du Sang (Annemasse).

The projects of the ERI20 team will be carried on the analysis of epidemiological associations between cancer and risk factors, in particular BC studied *per se* or in interaction with gene polymorphisms. Similarly, risk factors for type II diabetes are being investigated.

4.2.2 General characteristics of the EsMaestras cohort study

The EsMaestras study has enrolled 40,000 female teachers aged 35 years and over who are members of the Ministry of Education's (Secretaría de Educación Pública) economic incentives program (Carrera Magisterial) aimed at rewarding excellence in teaching in two representative states of Mexico: the state of Veracruz and the state of Jalisco. The first questionnaire was sent in 2006 and the follow up questionnaire will be sent in 2008. In addition, additional enrolment of 60,000 teachers from four other Mexican states is planed between 2008 and 2010.

Baseline characteristics have been obtained, as well as information on dietary intake, physical activity, self reported anthropometric measures, reproductive history, and early life factors, with focus on risk factors for chronic diseases, in particular cancer, NIDD and cardio vascular diseases. Pathological reports and blocks of breast tumor are being obtained for diagnostic confirmation.

Anthropometric measurements, mammography (to determine breast density), bone density, spirometry, biological samples, and further detailed information on physical activity, diet and early life factors have been obtained on a subsample of 2000 women. Blood samples have been aliquoted (plasma, serum, erythrocytes, buffy coat) and stored at –80°C for further analyses.

4.3 Lines of Research

The scientific program of the present proposal is organized into **different lines of research** including: *1) phenotyping of breast cancer tumor; 2) potential pathways that related BC and type II diabetes; 3) environmenytal determinants of both BC and type II diabetes in particular energy balance and dietary factors; 4) the role of hormones in both BC and Type II diabetes; 5) genetic determinants and gene environment interaction in BC and type II diabetes* These lines cover most of current and planned activities in both institutions and harmonization in the approach to address these issues will be conducted between the groups through this collaboration enriching the potential for scientific findings of relevance (possibility of replication of the findings)

4.3.1. Chronic diseases in women: Breast cancer and Type II diabetes

Breast cancer

BC is not a single entity. In particular tumors differ on their **histological type and hormone receptor status**. These characteristics are both prognosis and predictive factors. Histological types and hormone receptor status may further define groups of tumors that are etiologically distinct, as suggested by the fact that the associations between a number of risk factors and BC differ according to these characteristics(52-55). In both cohort studies, occurrence of cancer is self reported and further validated by pathology reports. In the E3N study, more than 96% of BC reports have been obtained so far. Information on estrogen and progesterone receptors and on histological types is extracted from these reports. In addition, collection of tumoral blocks is planed for a better characterization of tumors, using arrays.

Breast density has been identified as an intermediate outcome, predictor of BC risk. In Mexico, a large case control study has been conducted to determine the risk factors for breast density and its predictive values. In EsMaestras, mammography studies are conducted on a sub sample of the cohort and mammograms are being digitized. In the E3N study, it is planned to similarly digitize mammograms.

In both cohorts, **BC phenotype** will be better determined by using tumor histology and receptor status, and by considering breast density as an intermediate marker. This is important because risk factors are likely to differ by phenotype, thus conditioning public health recommendations and treatment.

Type II Diabetes

In both studies, diagnosis of type II diabetes is self reported by the participants. In E3N a validation of type II diabetes cases has been performed by requesting additional information to participants and their medical doctors. 94% of the self reported incident cases responded to the confirmatory questionnaire, and among them 76% were confirmed. In EsMaestras, we plan to use a similar validation process, however we currently have only identified prevalent cases of type II diabetes and conducted a direct assessment using biological measurements in a subsample of the cohort. Carbohydrate intake has been identified as a risk factor for BC in both the E3N cohort(56) and among the Mexican population(57) (case-control study). Further analyses to determine the **potential pathways that related BC and type II diabetes** are of major relevance. For example IGF levels in blood seem to be related to BC in premenopausal but not in postmenopausal women(58). However, mechanism for this association is still unknown. We plan to further investigate this potential association between type II diabetes and BC.

4.3.2. Environmental determinants of chronic diseases

4.3.2.1 Energy balance and endogenous hormones

Adult adiposity may be mediated by increased levels of estrogens (synthesized by adipocytes) or hyper insulinemia (which can act directly or by reducing IGF binding proteins). Work has been conducted at INSP as part of a large case control study to determine the relation between IGF and BC. Other biological markers such as adiponectin, a newly discovered protein secreted exclusively by adipoctytes seem to act as insulin sensitizers and might be involved in both type II diabetes and BC risk. We plan to determine the role of overweight and obesity, patterns of weight (abdominal or gynoid), age at onset of overweight/obesity, and markers of insulin status on the risk of the different types of BC among pre and post menopausal women, and on the risk of type II diabetes.

Early childhood fatness has been related to a lower risk of BC in the E3N study(26) and in some others but not all, therefore the evaluation of body build in childhood and adolescence is important. Both cohorts have collected information on body silhouette at various ages, giving the opportunity to evaluate how early body composition might affect risk. In particular we plan to evaluate the role of evolutions of body shape since childhood, physical activity, age at onset of regular cycles, alcohol consumption, socio-economic level during infancy in both the E3N and EsMaestras data. Whether such association is limited to certain types of BC will be explored.

Physical activity (PA) can affect hormonal levels, in particular by increasing sex hormone-binding globulin (SHBG), thereby reducing bioavailable estrogens. Both groups have a large interest in studying the impact of physical activity on BC and type II diabetes. Vigorous PA has been found a protective factor for BC in E3N(59) and in the Mexican population, but even moderate exercise appears to have a protective effect. Since increased PA appears to reduce insulin resistance and hyperinsulinemia, it might be of some importance in the association between BC and type II diabetes. In addition it is also important to determine how PA might influence breast density.

4.3.2.2 Dietary factors

Dietary pattern

Using the dietary pattern approach, studies have identified diet related to obesity and other chronic diseases. Individuals with higher intakes of soft drinks, French fries, and refined grains ("Western diet") appear to have higher BMI than those with higher intakes of dark bread, cereal, chicken and fruit. Some patterns have also been associated with specific biomarkers of the metabolic syndrome and of inflammatory reaction. Such an approach will be used in both cohorts to categorize diet in each country, in order to assess if specific patterns are responsible the increase in risk of breast cancer and diabete.

Food and nutrients, and nutrigenomics

We will focus on food items and nutrients likely to play a role on the genesis of both diseases (BC and type II diabetes) such as

- the insulin resistance pathway, for instance foods with *high glycemic index*, and foods with high fiber content
- the one-carbon metabolic pathway (*folate, and vitamins B-6 and B-12,* and their interaction with the methylen-tetrahydrofolate reductase (MTHFR) gene polymorphism), involved in epigenetic expression and DNA repair.
- the lipid profile of the diet, in particular omega-3 PUFAs, and trans fatty acids that seem to influence transcription factor activity, gene expression, signal transduction pathways, estrogen metabolism, and mechanisms associated with insulin sensitivity.

- phytoestrogens, isoflavones and lignans/enterolignans.
- meat because of the potential use of hormonal compounds in its production.
- organochlorine and other pesticides

Biomarkers of diet
Both counterparts have nutritional laboratories, with expertise in fatty acids and carotenoids in France, and in a number of other micronutrients (folate, and vitamins B12, E and D) in Mexico.

Metabolic biomarkers
Collaborations with laboratories with expertise on insulin, C peptide, IGF1, IGFBP3 have been developed in France and Mexico.

4.3.2.3. Hormone levels

The French group is discussing collaboration with existing laboratories to determine sex steroid hormone levels, in order to study their association with:

- breast density,
- BC characterized by histological type and hormone receptor status,
- Type II diabetes

and interactions with known BC and type II diabetes risk factors.

The EsMaestras study is collecting blood samples and information relevant to determine time of sampling during the menstrual cycle in order to estimate the role of hormonal levels on the risk of BC.These samples will be analyzed in France at the collaborating laboratory of the French research group.

4.3.3. Genetic determinants

In Mexico, almost half (41.8%) of all BC cases occur before age 50 years in contrast with French women where the median age at diagnosis is 61. Most Mexican women present with BC at a late stage. The elucidation of genetic and environmental factors involved in breast cancer development in Mexican women is essential. The BRCA1 and BRCA2 gene mutations confer a very high susceptibility to breast cancer. So far, very few studies have been performed in Mexico. However, recurrent mutations have been found suggesting that a founder effect may exist in this population. Therefore, we will comprehensively investigate all types of mutations in BRCA1 and BRCA2 in Mexican women with breast cancer within the case control study. Furthermore, Maor et al.(60) recently observed that IGF-I enhances BRCA1 promoter activity, so it has been suggested that the effect of IGF-I on mammary gland cells may be mediated through BRCA1, and aberrant IGF signaling may have implications on breast cancer pathogenesis..

Cohort studies have shown that type II diabetes has been associated with an increased risk of BC (Summary relative risk of 1.25; 95% CI 1.19–1.31)(48). Activation of the insulin and insulin-like-growth-factor pathways, and impaired regulation of endogenous sex hormones, are among the suggested mechanisms. High levels of insulin-like growth factors, IGF-I (Insulin like growth factor I) and IGF-II, have been associated with an increased risk of BC through their role in growth and differentiation of the mammary gland. Disruption of the IGFs pathway balance has been implicated in the etiology and progression of the disease. The biological actions of the IGFs are mediated, in part, through the IGF-I receptor (IGF-IR). It

has been observed that estrogens stimulate the expression and activity of IGF axis components. Research on genetic polymorphisms in the mentioned pathways is relevant in order to comprehensively understand the association between type II diabetes and BC risk.

Regarding genetic admixture, latino/hispanic populations are known to be of mixed European, Native American and African ancestry. Recently, it has been proposed that there are several different BC diseases according to their histopathology and to the age at presentation. It has been hypothesized that these differences of BC are due, in part, to complex associations between genetic and environmental BC risk factors.

While the identification of mutations in BRCA1/2 genes has explained a substantial proportion of early-onset BC, little is known about common genetic variants associated with sporadic disease. Whole genome studies enable analysis of hundreds of thousands of SNPs in order to identify common genetic variants associated with sporadic cases. Recently, Hunter at al.(61) identified alleles in FGFR2, a tumor suppressor gene, associated with the risk of sporadic postmenopausal BC in women self-described as being of European ancestry from the Nurses'Health Study (NHS) cohort. In addition, Cox et al.(62) within the Breast Cancer Association Consortium (BCAC) (which includes EPIC and therefore a number of E3N cases) conducted a combined case-control analyse, which found a common coding variant in CASP8 D302H associated with BC risk. They found odds ratios (OR) of 0.89 (95% CI 0.85–0.94) and 0.74 (95% CI 0.62–0.87) for heterozygotes and rare homozygotes respectively, compared with common homozygotes. Collaborative studies are necessary to identify low-penetrance susceptibility variants. The collaboration between the French and the Mexican group will permit to merge data in order to achieve sufficient sample sizes to detect more modest effects of genes related to pre-and postmenopausal women

The Mexican group has already a collaboration with US and Canadian laboratories to identify specific genetic pathways related to the risk of BC in Mexican women, the role of genetic admixture and of its interaction with environmental factor (diet, physical activity, use of hormonal treatments, biomarkers of insuline metabolism and inflammation etc...) on the risk for BC. Similar determination and analyses are also planned to be conducted in the E3N cohort.

5. ORGANIZATION AND WORKING PLAN

5.1 Organization

We are planning to establish a coordinating team with one responsible person from each country who will communicate with the other researchers in their group and will be in charge to plan and monitor the development of the collaboration in term of administrative request from institutions involved, scientific and technical exchanges and seek external funding sources.
For each research topic we will establish an international team with a responsible from each research group.

5.2 Type of activities

A major emphasis of our project is to promote and support scientific and technical exchanges between the two groups. For this we plan to promote and support the inter-laboratory visits of senior scientist, the exchange of junior scientists, co-training and thesis supervision of doctoral students, development of common manuscript and development of joint research project for international funding within the context of innovative research in the

area of epidemiology of chronic diseases in women.

5.3 Chronogram of activities

We are presenting activities for the short term, medium and long term.
Some collaborative activities and exploration of the feasibility of this project has already taken place.

1. Short term activities

January 2006 – August 2007: Exploratory/feasibility phase

- Definition of areas of common interests and first strategic plan (visit of IR to France)
- Exchange of junior researcher from INSP to ERI 20 (Martin Lajous, Mexico)
- Short term visits and exchanges including mutual invitations to seminar and internal meetings of major studies (IR to France and FCC to Mexico)

This phase has been successfully completed (see appendix 1) and has shown the feasibility of the project. Collaborative lines have been defined.

September 2007 - August 2008: Starting period: consolidation of the collaboration

In this phase, the existing collaboration has been consolidated on a longer term basis, with the exchange (Training fellowship) within the doctoral thesis of Alban Fabre from ERI 20 to work with IR (INSP, Mexico) and the visit of IR (INSP Mexico) to the ERI 20 to further define a working research plan focused on the priorities and to set up the conditions for its implementation.

2. Medium term activities

September 2008 - August 2010: Development of activities of common interest and increasing competitiveness

- Developing a food composition data base by sharing nutrient food composition tables on phytoestrogens, *trans* fatty acids, and other nutrients of interest
- Developing a table of glycemic index for the foods included in the FFQ used by both groups.
- Sharing the computerized program (developed by the Mexican group) to quantify breast density in mammograms, and training French technicians
- Planning and conducting the analysis of the relationship between glycemic index and glycemic load, and BC risk in the E3N study and the large Mexican case-control study
- Planning and conducting the analysis of the use of oral contraceptive and HMT in association with breast density and breast cancer risk
- Planning and conducting the analysis of the association between metabolic risk factors for type II diabetes (insulin, IGF1, IGF3, cholesterol) and breast density and breast cancer
- Organizing a meeting to discuss the use of biological markers and the standardized techniques of measurements in relation to breast density and breast cancer
- Based on prior findings, discussing further hypotheses to provide a better understanding of the role of nutrition and hormones in breast cancer and type II diabetes
- Development of common manuscripts

This step will reinforce the collaboration between the two teams sharing similar research interest and analytic plan. Also, comparing results between studies will provide more insights about potential mechanisms. In this step, some analyses will involve data from the E3N and EsMaestras studies, and others will used data from the large Mexican case-control study (CAMA) conducted by the INSP.

3. Long term collaboration- Development of innovative research and strengthening of the collaborative structure

At longer term, the EsMaestras study will be recruiting teachers from other Mexican states to reach 100,000 women and information from several follow up questionnaires (every two

years) will be available. Future research includes to:

- Plan and conduct analyses of nutrients biomarkers in relation to breast density, breast cancer and type II diabetes in particular folate, vitamin B12, vitamin D, and omega3-PUFAs.
- Organize a meeting focusing on genetic aspects with researchers associated with genetic programs in France and Mexico, and collaborative groups (USC, CANADA) in order to explore potential for collaboration and replication studies with special focus on genes involved in the insulin, one-carbon, and vitamin D pathways, and on gene- nutrition interaction.
- Develop coherent research plan involving the hormonal, nutritional and genetic aspects, and evaluate the best approach to strengthen the collaboration and the potential funding of common projects.

5.4 Scientific and technical exchanges

1) Sofware to measure mammographic features: The INSP has the expertise in the measurement and interpretation of breast density. UNAM and INSP have worked jointly to develop a software to measure mammographic features (breast density). They will help training a technician in the French group to measure the mammographic features. Breast density has been associated with BC risk. Different types of hormonal treatments, diet, and IGF levels may diversely affect breast density, and therefore play different roles in the risk of BC.
2) The French group has international expertise in analysing prospective data on use of hormonal treatments and has conducted several analyses to determine the impact of different combinations of estrogen and progestins on the risk of various chronic diseases. Large variety of types and routes of administration of both estrogen and progestins have been used in France for a long time. This expertise will be transferred to the Mexican group who has been collecting data on use of specific hormonal therapies in several studies.
3) Both teams have a long lasting international expertise in nutrition and physical activity in relation with chronic diseases. Several members of both teams are graduated from one of the most prestigious Schools (Harvard School of Public Health, Cornell, London School of Hygiene and Tropical Medicine) with ongoing international research links. Scientific material including food composition tables for specific nutrients such as phytoestrogens and glycemic index has been exchanged in the past and led to common publications.
4) Laboratories: The Mexican group could benefit from the existing labs on fatty acids and carotenoids developed in France at the Institut Gustave-Roussy. The French group could benefit from the existing lab in Mexico on several micronutients (folate, vitamin B12, vitamin E etc.) with a potential for exchange of standards, techniques and personnel. The French group is developing collaborations with existing labs on steroid hormones, which could perform the analysis of Mexican samples.
5) The Mexican team has an international expertise on environmental health. Several environmental exposures have been linked to chronic diseases, in particular organochlorine products. While their impact on hormone-dependent diseases and type II diabetes is still debated, we are planning to jointly further explore their effect, benefiting from the large range of exposure resulting from the pooling of the Mexican and French population. Organochlorine had been used till recently in Mexico and blood levels are relatively high compared to levels in the French population.
6) We will take advantage of the expertise of the French group in implementing the E3N longitudinal cohort in France, to help the Mexican group develop the EsMaestras cohort study, which design is very similar, relying on a population of similar size, occupation,

educational level, and geographic spread. All the logistic experience in handling data recording and data management of large numbers of observations will be shared, as well as experience of data analysis of longitudinal studies.

7) Scientific exchange
Student exchanges have already taken place between the two groups resulting in international publications. A doctoral student form the E3N team is currently at he INSP working on Mexican data on BC and use of hormonal treatment. In addition several visits of the PIs in their partner laboratory have already occurred, during which scientific presentations and writing of scientific papers have been performed.
Further exchanges are planned in the framework of the present collaborative project to further strengthen the scientific expertise of both groups. Both teams have large experience in networking at the national and international levels. At the national level, the French team works in collaboration with a large number of research laboratories; at the international level, the French team represents the French part of the EPIC cohort study. The Mexican team has developed over the year a strong national and international network with local university and health systems and is involved in a number of international collaborations with different institutions in the US (Harvard, UCSF, MOFFIT Center, and NIH), England and Latin America.

5.5 Indicators for evaluation

Evaluation will be based on the accomplishment of the activities planned and the interaction between members of both group, in particular 1) interchange of scientists; 2) scientific document developed jointly; 3) technical exchange; 4) joint organization of international workshops; 5) development of common research programs, and increase in the quality and impact of research.

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Annexe B

ENGAGEMENTS FINANCIERS POUR 2009

Inserm :

Sur le budget de l'Inserm :
- Un poste de post-doctorant (1 temps plein x 3 ans) : 56k€
- Déplacements (France-Mexique) : 5k€

Sur le budget Inserm-ERI20 :
- Accès aux logiciels, bureaux et lignes téléphoniques des partenaires mexicains : 1k€

INSP :

- Mise à disposition d'un logiciel développé par l'équipe mexicaine pour l'analyse d'images de densité mammaire et formation de l'équipe française : 10k€
- Un voyage par an pour un chercheur mexicain venant à l' ERI20 (billet aller/retour et séjour de 5 jours) : 2k€

Co-direction de recherche pour un étudiant français en thèse de Doctorat, Guy Fagherazzi, assurée conjointement par Françoise Clavel-Chapelon et Isabelle Romieu.