Universidade Federal do Rio Grande do Sul
Faculdade de Medicina
Programa de Pós-Graduação em Epidemiologia

Avaliação da História Familiar de Câncer como Co-Fator Associado ao Aumento do Risco de Câncer de Cérvice Uterina

Alice de Medeiros Zelmanowicz

Orientadora: Prof[a] Dra. Maria Inês Schmidt
Co-orientador: Allan Hildesheim, Ph.D.

Tese apresentada ao Programa
de Pós–Graduação em Epidemiologia
como requisito parcial à obtenção do
título de Doutor em Epidemiologia.

Porto Alegre
2004

“There is no source of absolute truth
(in pathology), only advancing degrees of expertise
correlated with decreasing amounts of (diagnostic) error.”

Schiffman, M, 2001

AGRADECIMENTOS

Realizar uma tese de doutorado é mais do que assistir alguns cursos, analisar bancos de dados, escrever alguns artigos. É um processo de crescimento pessoal, é um amadurecimento. Por este motivo, quando se chega no momento de defendê-la publicamente, tem-se tantas pessoas para agradecer e reconhecer a importância neste processo. São muitas, seria injusto esquecer alguém e este, certamente, não é o final deste processo. Algumas eu não poderia deixar de fazer uma especial menção:

- Ao **Dr. Allan Hildesheim**, Investigador, Division of Cancer Epidemiology and Genetics, National Cancer Institute, co-orientador desta tese, que soube ser orientador quando necessário e amigo quando preciso com a sua enorme capacidade e dedicação.

- À **Dra Maria Inês Schimdt**, orientadora desta tese e coordenadora do Programa de Pós–Graduação em Epidemiologia, da Universidade Federal do Rio Grande do Sul, que com tanto empenho tem se dedicado a tornar este um programa de primeira linha.

- Ao meu marido, **Prof. Gilberto Luiz Sanvitto** que, mais que um orientador, mais que um companheiro, é um exemplo para mim.

- Ao **Dr. Airton Stein e Dr. Sotero Mengue**, por todas as formas de incentivo e confiança.

- Ao meus **colegas do Programa de Pós-graduação** que sempre me incentivaram a seguir os caminhos que escolhi.

- À rede de amigas que estiveram ao meu lado, me ajudando de uma forma ou outra, compartilhando minhas dificuldades, vibrando com nossas conquistas, em especial, **Ana Luiza Abuchaim**, **Mariana Hildesheim**,

Lúcia Scalco, **Lídia Medeiros**, **Elisabete de Medeiros Zelmanowicz**, **Clady Maria Sanvitto**, **Marianne Zelmanowicz de Abreu**.

- Ao meu pai, **Dr. Rolf Udo Zelmanowicz**, por ter me mostrado que é importante querer ir sempre mais adiante.

- Ao Diretor do Centro de Câncer, **Dr. Ênio Utz**, e ao diretor do Hospital Santa Rita, **Dr. James Fleck**, do Complexo Hospitalar Santa Casa de Porto Alegre por terem cedido minhas horas de dedicação para este empreendimento.

- Aos **funcionários** do Programa de Pós-graduação em Epidemiologia e da Assessoria Científica da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul por sua dedicação.

Dedico esta tese aos meus filhos, João Pedro e Mateus

SUMÁRIO

LISTA DE ABREVIATURAS

HPV – Papilomavírus Humano ou Human Papilomavirus

IARC – International Agency for Research on Cancer

INCA – Instituto Nacional do Câncer

IBGE – Instituto Brasileiro de Geografia e Estatística

APVPP – anos potenciais de vida produtiva perdidos

APVP – anos potenciais de vida perdidos

EUA – Estados Unidos da América

NIC – Neoplasia intra-epitelial

LIEBG – Lesão intra-epitelial de baixo grau

LIEAG - Lesão intra-epitelial de alto grau

DNA – Ácido Deoxidoribonuclêico

OR – Odds Ratio ou Razão de Chances

ACO – Anticoncepcional Oral

AIDS – Síndrome da Imunodeficiência Adquirida

HSV - Vírus Herpes Simples

HLA – Antígeno Leucocitário Humano

RESUMO

O câncer de cérvice uterina é um problema de saúde pública na maioria dos países em desenvolvimento e também nos países desenvolvidos. Não só porque acomete mulheres relativamente jovens mas também porque seria prevenível caso um programa de rastreamento fosse factível de ser implantado em grande escala.

Hoje se conhece muito sobre a patogênese deste câncer e de suas lesões precursoras. É reconhecido, por exemplo, que a infecção pelo Papilomavírus Humano (HPV) é imprescindível neste processo. Porém a grande maioria das mulheres infectadas por este vírus não evolui para câncer. Fatores associados, co-fatores, são importantes tanto na resposta ao agente infeccioso, na persistência da infecção, quanto na evolução de lesões precursoras para lesões invasivas.

Alguns destes co-fatores já são conhecidos, fumo, alta paridade, uso de anticoncepcional oral por um longo período, co-infecção pelo HIV. Outros estão sendo investigados. Um dos fatores menos estudados são as características do hospedeiro e sua capacidade de resposta à infecção e ao processo de malignização. História familiar traduz características genéticas, ambientais e culturais de um indivíduo. História familiar de câncer é fator de risco em maior ou menor intensidade para a maioria dos cânceres. Porém, este co-fator tem sido pouco estudado em relação ao câncer de cérvice.

O objetivo desta tese é examinar a associação entre história familiar de câncer e risco para câncer de cérvice. Apesar de alguns estudos de base populacional e outros em amostras hospitalares terem sido feitos, nenhuma sistematização das publicações disponíveis foi ainda feita. Uma revisão dos artigos que analisavam esta associação foi feita e confirmou um excesso de risco aproximadamente duas vezes maior entre as mulheres que tem história familiar de câncer de cérvice entre parentes de primeiro grau. Além disso, foi feita a análise de dois bancos de dados, um caso-controle na região leste dos Estados Unidos e um estudo transversal em uma região da Costa Rica. Nos dois estudos, foi evidenciada uma associação positiva de história de câncer de cervice em familiares de primeiro grau e risco para câncer de cérvice.

Com isso, conclui-se que história familiar de câncer é um co-fator para câncer de cérvice uterina.

ABSTRACT

Cervical cancer is an important public health problem not only in most developing countries but also in industrialized ones. That is so not only because it is common among relatively young women but also because it could be prevented should screening programs be implemented in large scales.

Nowadays, much is known about the pathogenesis of this cancer and its precancerous lesions. It is known that infection of the human papillovirus (HPV) virtually occurs in all cases. However, the majority of women infected by this virus do not develop cancer. Thus, related factors, co-factors, are very important in relation to the response to the infectious agent, to the persistence of the infection, and to the progression of precancerous lesions into invasive lesions.

Some of these co-factors are well known; smoking, high parity, use of oral contraceptive for long periods, and co-infection with HIV. Other co-factors are being investigated. One of the factors least studied is the feature of the host and its capacity to respond to the infection and malignancy. Family history conveys the genetic, environmental and cultural characteristics of the individual.

Family history of cancer is a greater or smaller risk factor in almost all cases of cancer. However, this co-factor has not been thoroughly studied as regarding cervix cancer.

The objective of this thesis is to examine the association between family history of cancer and cervix cancer risk. Although some population-based studies as well as others - some with hospital samples – have been carried out, there is no systematic review of such studies. A systematic review of the 20 articles that analyzed this association was performed and it confirmed excess in risk, approximately two fold, among women with relatives of first degree with family history of cervix cancer. Furthermore, the analysis of two data bases, one case-control study in the east of the USA and a cross-sectional study in a region of Costa Rica. In both studies there was a positive association of history of cancer in first-degree relatives and risk for cervix cancer.

Hence, this study concludes that cancer family history is a co-factor for uterine cervix cancer.

INTRODUÇÃO

O câncer de cérvice uterina representa um importante problema de saúde pública. Ele é responsável pela morte de um grande número de mulheres, principalmente em países em desenvolvimento. Este é um câncer que acomete mulheres jovens e na ausência de um programa de detecção precoce de cobertura ampla e contínua, este tumor é diagnosticado muito tarde e causa a morte da maioria das pacientes.

A universalidade do acesso à detecção precoce e a medidas preventivas é cara e para a maioria dos países pobres, os mais acometidos, inviável do ponto de vista econômico e logístico que dê suporte a coleta, transporte e interpretação de material a ser analisado. Nos países que implementaram programas efetivos de detecção precoce através da citologia cervical (exame de Papanicolau) a incidência e a mortalidade associada a este tumor diminuíram significativamente (Gustafsson et al, 1997). Porém, nos Estados Unidos, um programa como este custa anualmente em torno de cinco bilhões de dólares (Jemal et al 2003)

A identificação das mulheres de maior risco para desenvolver este tumor pode aumentar a efetividade de medidas preventivas e de programas de detecção precoce ao focar seus recursos naquelas que mais se beneficiariam de tal esforços.

Reconhecer grupos de alto risco através da compreensão da fisiopatologia e identificação de fatores e co-fatores de risco é fundamental neste processo. Estudos epidemiológicos dão a oportunidade de se analisar estas mulheres e identificar tais fatores e sua relação com a história natural desta neoplasia. História familiar de câncer é fator de risco para a maioria dos cânceres. A associação deste co-fator e câncer de cérvice uterina é uma questão ainda não completamente definida nos estudos disponíveis.

Esta tese é composta de uma revisão da literatura sobre câncer de cérvice uterina, fatores e co-fatores de risco e de dois artigos originais, onde a associação entre história familiar de câncer e câncer de cérvice uterino é avaliada. O primeiro artigo faz um levantamento sistemático dos artigos que abordam a relação da história familiar de câncer e o risco para câncer de cérvice. O segundo artigo avalia a possível participação da história familiar de câncer de cérvice como co-fator associado ao aumento de risco do câncer de cérvice em estudos epidemiológicos que analisaram fatores de risco para este tumor.

Capítulo I – Revisão da Literatura

1. Epidemiologia

1.1. Distribuição Mundial:

O câncer cervical é a segunda causa de morte por câncer entre as mulheres no mundo, sendo que 80% destas mortes são nos países em desenvolvimento. Aproximadamente, 288 000 mortes ocorrem no mundo anualmente decorrente desta neoplasia, sendo 77 000 na América Latina (Drain et al., 2002).

Estima-se que aproximadamente 471 000 novos casos foram diagnosticados no ano de 2000 (Parkin et al., 2001). As maiores incidências mundiais acontecem em alguns países da América Central e do Sul, com o Haiti sendo o país com maior incidência no mundo (IARC, 2000), e no leste e sudeste da África.

A falta de recursos preventivos e a necessidade de medicina de alta tecnologia, como serviços de oncologia clínica e cirúrgica e radioterapia para o tratamento das doenças avançadas, são os fatores responsáveis pelo alto custo humano e financeiro associado a esta doença e conseqüentemente a dificuldade de países menos favorecidos de lidar com este problema de saúde pública.

1.2. Distribuição no Brasil:

No Brasil, o Ministério da Saúde estima que 3953 mulheres morreram em 2000 decorrente de câncer de cérvice e está previsto serem diagnosticados mais de 16 000 novos casos no ano de 2003, perfazendo 10% dos cânceres entre as mulheres (INCA, 2003). Aparentemente, este número vem crescendo o que pode ser decorrência tanto de um aumento real do número de novos casos e da mortalidade quanto de um melhor registro desta doença.

Também no Brasil, como em outros países em desenvolvimento, a maioria dos casos de câncer de cérvice é diagnosticada nos seus estágios mais avançados e segundo os dados gerados pelos Registros de Câncer Hospitalares, metade das pacientes é diagnosticada nos estágios III e IV (INCA, 2003). Esta realidade é um reflexo da dificuldade de implementar programas de detecção precoce do câncer de colo uterino.

Estima-se que mais de 35 milhões de mulheres de 25 a 60 anos estariam em idade de realizar exame preventivo de câncer de cérvice, segundo o censo do IBGE de 2000. Naquele ano, foram realizados 3,9 milhões de exames além dos 8 milhões que usualmente o Sistema Único de Saúde faz no seu programa Viva Mulher, após um esforço significativo de intensificação do programa (INCA, 2003). Porém, este esforço não refletiu em queda da taxa de incidência ou mortalidade.

As taxas de incidência e mortalidade desta neoplasia variam enormemente nas diversas regiões do país, como pode ser visto a seguir segundo estimativa do INCA para 2003, (taxa bruta por 100 000 mulheres). Nestes números estão incluídos casos de câncer do útero, porção não especificada.

Tabela 1. Estimativas de taxas de incidência e mortalidade por câncer de cérvice por região. Brasil. 2003 - Taxa bruta por 100 000 mulheres

Região	**Novos Casos**	**Óbito**
Norte	15,77	6,86
Nordeste	16,11	5,45
Centro-oeste	36,19	7,50
Sudeste	26,03	7,61
Sul	25,53	9,74
Brasil	**23,10**	**7,25**

Fonte: INCA, 2003

Segundo as estimativas para 2003, Cuiabá será a capital com a maior taxa bruta de incidência por esta neoplasia (52,54 novos casos/100 000 mulheres), porém a maior taxa de óbito entre as capitais brasileiras é em Belém do Pará, 16,10/100 000 mulheres (INCA, 2003).

Levando em consideração as limitações decorrentes de estudos baseados em atestados de óbito, dados referentes ao Rio Grande do Sul para os anos de 1979 a 1998 demonstraram um aumento linear do coeficiente bruto e padronizado de mortalidade por esta neoplasia neste estado. No período inicial da observação tem-se uma taxa bruta de 5,3 mortes por 100 000 mulheres e ao final, em 1998, 9,6 por 100 000, um incremento de mais de 80 % no período (Kalakun, 2002). Neste estudo, calcula-se que a média de anos potenciais de vida produtiva perdidos (APVPP) foi de 9,8 (+ - 0,96) anos e anos potenciais de vida perdidos (APVP) 21,9 (+- 1,33) anos.

2. Classificação Histológica

O tipo histológico mais comum do câncer de cérvice é o carcinoma epidermóide. Nos EUA, perfazem mais de 80% dos casos (Chan, Sung e Sawaya, 2003). Este tipo de câncer se origina nas células escamosas da cérvice, aproximadamente 98% na junção escamocolunar e suas áreas adjacentes (Zona de Transformação). Tumores avançados podem se apresentar ulcerados ou nodulares (apresentação endofítica), ou polipóide ou papilares (apresentação exofítica). Os primeiros tendem a se desenvolver para dentro do canal endocervical e invadir as porções inferiores do útero. Seus sub-tipos histológicos dividem-se basicamente entre carcinomas queratinizados e não-queratinizados.

A incidência do adenocarcinoma de cérvice é variável, sendo descrito freqüências de 3 a 34% dos tumores invasivos do colo uterino. Porém, em vários países, o seu diagnóstico tem crescido absoluta e relativamente, particularmente entre mulheres jovens. Comumente (mais de 70% dos casos) são compostos por células endocervicais (tipo mucinoso), mas podem se assemelhar com glândulas do tipo endometrial (variante endometrióide). Outra apresentação, também menos freqüente, é o carcinoma adenoescamoso quando se encontram componentes glandulares e pavimentosos. (Wright et al, 2001).

Numa série de 1139 casos de carcinoma de cérvice em um hospital público de Porto Alegre, RS, (Cambruzzi, 2003, dados não publicados), 908 casos eram carcinomas epidermóides, 229 adenocarcinomas e 2 carcinomas mistos (um adenoescamo e um adenóide basal). Setenta e dois (31,5%) casos de adenocarcinomas apresentavam lesões intra-epiteliais escamosas associadas.

Os carcinomas cervicais podem ter uma evolução mais rápida do que usual, independente do tipo histológico. Segundo Hildesheim e colaboradores (1999), mulheres com a apresentação do câncer de cérvice reconhecida como tumor de intervalo (*rapid-onset disease),* que é diagnosticada entre os intervalos de exames de rastreamento (3 anos ou menos), mais freqüentemente têm tumores com envolvimento glandular (adenocarcinoma ou adenoescamoso) quando comparado com mulheres com tempo de diagnóstico usual, apesar que esta associação pode ter sido resultado de exames citológicos prévios falso-negativos.

3. Patogênese

O câncer de colo uterino é um dos tumores que tem a sua carcinogênese mais amplamente estudada e elucidada. O fato de se reconhecer o Papilomavírus Humano (HPV, na sua sigla em inglês) como fator necessário e causal para este tumor capacitaram os pesquisadores a compreender as fases pré-malignas e suas transformações neoplásicas.

3.1. Nomenclatura:

A idéia de que o câncer de cérvice representa o final de um processo de alterações progressivas do epitélio com um espectro de lesões precursoras identificáveis é do período do final do século XVIII. Desde então, diversas nomenclaturas e tentativas de sistematização destas alterações foram propostas. Embora as modificações da nomenclatura e a falta de uma terminologia uniforme têm criado grande confusão entre patologistas, ginecologistas e, mais recentemente, epidemiologistas, há um reconhecido progresso no sentido de correlacionar o padrão patológico das lesões com o seu significado biológico. O progressivo entendimento da fisiopatogenia da infecção pelo HPV permitiu reconhecer as alterações celulares da cérvice uterina como uma resposta a esta infecção e sua persistência e incorporação ao genoma da célula cervical.

Ao infectar a cérvice uterina, um ou mais dos 40 tipos de HPV que infecta o trato ano-genital promove alterações citoplasmáticas e nucleares, que na grande maioria dos casos são autolimitadas. Estas lesões são as que antigamente se identificava como *Koilocytosis,* displasia leve ou neoplasia intra-epitelial 1 (NIC 1).

Nos raros casos (Schlecht et al, 2003) em que a infecção persiste, alterações nucleares mais severas podem ser identificadas e têm um real potencial de malignização se não forem tratadas. São as chamadas lesões de alto grau, também identificadas como displasia moderada ou severa, carcinoma *in situ* ou NIC 2 ou 3. Nas lesões de alto grau, DNA viral pode ser identificado nas lesões e os tipos de HPV envolvidos são quase que exclusivamente os identificados como do tipo oncogênico (principalmente 16,18, 31, 45 e 56).

Esforços para sistematizar e unificar a classificação das lesões cervicais têm sido feitos desde 1988 com o Sistema de Bethesda de Citologia Cervical e com a

sua última atualização (Solomon et al., 2002). As alterações são divididas em lesões intra-epiteliais de baixo grau, aquelas que são uma tradução da infecção por HPV, e lesões intra-epiteliais de alto grau, aquelas que representam uma persistência desta infecção principalmente por HPV do tipo oncogênico e como tal com maior potencial de malignização. Esta classificação tem sido proposta para que seja usada nos diagnósticos citológicos e histológicos, já que para ambas as técnicas esta forma traduziria mais adequadamente o significado biológico e clínico da lesão. Cada vez um maior número de centros utilizam esta nomenclatura para identificar as alterações cervicais desta forma. Porém, esta terminologia está em contínua evolução, proporcional ao progresso do conhecimento desta doença, e assim várias publicações ainda utilizam graus de displasia ou neoplasia intraepitelial para designar os seus desfechos.

3.2. Lesões Precursoras:

O carcinoma do sub-tipo histológico epidermóide, por ser mais freqüente, serve de base para os modelos descritivos da patogênese do câncer cervical.

O epitélio celular responde à infecção pelo HPV através de uma progressiva perda de diferenciação. Proliferação celular, maturação e atipia citológica são as características principais das lesões intra-epiteliais escamosas. Aumento da atividade mitótica e presença de figuras mitóticas anormais também são típicas. A categorização em três níveis que as neoplasias intra-epiteliais (NIC) traduziam baseava-se na proporção de epitélio ocupado por células com perda de maturação progressiva. Este aumento de células alteradas se dá da membrana basal em direção à superfície epitelial. Quando estas alterações ultrapassam o terço basal do epitélio o diagnóstico muda de lesão escamosa intraepitelial de baixo para alto grau (NIC 1 para NIC 2/3). A ocupação total do epitélio é característica do carcinoma *in situ.* Este espectro de alterações ainda não tem um ponto de corte definitivo (Kurman, 2001).

Apesar de se reconhecer que todo o carcinoma de cérvice deve ser precedido por lesões pré-malignas, pouco se sabe sobre a história natural das lesões precursoras do adenocarcinoma de cérvice. Desde 1952, quando Helper (Kurman, 2001) descreveu células atípicas com glândulas estruturalmente normais junto a adenocarcinomas de cérvice, reconhece-se o conceito de adenocarcinoma *in situ.*

Por analogia ao carcinoma epidermóide, tem-se tentado estabelecer uma classificação que traduza um espectro de alterações pré-malignas precursoras ao adenocarcinoma *in situ* e à lesão invasiva que ordene as lesões em graus progressivos de displasia celular. Porém, devido a sua raridade, o seu significado clínico é incerto e a denominação geral de atipias glandulares endocervicais é mais aceita por alguns autores (Kurman, 2001). Com o progressivo uso de escova endocervical para coleta de material e com o aprimoramento técnico para reconhecer estas lesões, estima-se que a melhor identificação desta doença resultará no aperfeiçoamento da sua nomenclatura.

Basicamente, as células do adenocarcinoma de cérvice *in situ* se caracterizam por apresentar semelhança com o adenocarcinoma sem apresentar sinais de invasão tecidual. A razão núcleo:citoplasma pode estar aumentada e figuras de mitoses são comuns (Kurman , 2001).

3.3. Carcinoma Invasivo:

Estudos moleculares *in vitro* têm permitido um melhor entendimento dos mecanismos de como o HPV induz as células da cérvice uterina à transformação neoplásica após a sua persistência na cérvice uterina. HPV do tipo oncogêncio, como o 16 e 18, tem a capacidade de produzir proteínas estimuladoras do crescimento e da transformação (oncoproteínas) que interagem com o sistema regulador da célula, alterando-o. Provavelmente os mecanismos de como o HPV desenvolve a persistência da infecção e a progressão para malignidade são distintos.

Este modelo de patogênese não explica completamente a transformação maligna da célula infectada pelo HPV, já que apenas uma pequena parte dos indivíduos com infecção persistente evoluem para uma transformação maligna. O papel de co-fatores neste processo provavelmente é de fundamental importância.

4. Fator de Risco - Infecção pelo HPV

Os primeiros estudos que testaram a associação entre HPV e lesões precursoras e câncer de cérvice não foram capazes de demonstrar uma associação forte e consistente. Além disso, a relação entre exposição ao HPV e práticas sexuais também não era sistematicamente estabelecida, fator este reconhecidamente relacionado a estas lesões. Porém, com o desenvolvimento tecnológico, testes mais acurados de detecção do HPV foram utilizados nos estudos epidemiológicos e ficou claro que HPV era um fator essencial na patogênese das lesões neoplásicas do colo uterino e por ser sexualmente transmissível, ficou claro também que atividade sexual era um fator substitutivo de exposição à infecção pelo HPV (IARC, 1995).

Atualmente, a associação entre o HPV e o câncer de cérvice e suas lesões precursoras apresentam todos os critérios de causalidade descritos por Bradford Hill, em 1965 (Bosch e de Sanjose, 2003), como se segue:

a) Temporalidade:

Para a maioria dos autores, temporalidade é uma característica essencial para se determinar efeito causal. Estudos de coorte de mulheres sem alterações citológicas, com achados laboratoriais compatíveis com infecção pelo HPV ou não, quando seguidas por tempo suficiente demonstraram um risco aumentado de desenvolver lesões pré-neoplásicas ou câncer após 5 ou 10 anos depois de se detectar a evidência da infecção. (Sherman et al., 2003 e Schlecht, 2003).

b) Força de Associação e Consistência:

Todos os estudos que testaram a associação entre a infecção pelo HPV e o desenvolvimento de câncer de cérvice e suas lesões precursoras demonstram uma associação consistentemente positiva com riscos relativos aumentados que variam de 50 a 500 quando comparados com controles. Esta associação é reproduzida em estudos de diferentes populações e metodologias aplicadas. Um estudo em que espécimes de câncer cervical invasivo de pacientes de diversos países foram analisados, demonstrou DNA de HPV dos tipos oncogênicos em mais de 93% dos tumores (Bosch et al., 1995). Quando as amostras negativas para HPV foram re-

analisadas com um método mais sensível, a associação entre identificação de DNA de HPV oncogênico e câncer cervical foi superior a 99% (Walboomers et al,1999).

c) Especificidade de Associação e Analogia:

O vírus Papiloma é amplamente distribuído na natureza. Existe descrição de Papilomavirus bovino, canino, entre aves, coelhos e veados, além de humanos. Porém, eles são altamente espécie-específico, infectando apenas uma espécie. Dentro de uma espécie, vários tipos e sub-tipos podem existir. Existe mais de 100 tipos humanos e mais de 40 tipos de HPV que infectam a região ano-genital, porém todos têm alta especificidade com respeito ao epitélio que infectam e o tipo de lesão que desenvolvem. Ele é um vírus *epiteliotrófico* que predominantemente infecta a pele e a mucosa, produz proliferação tecidual e, em certas condições, tem potencial de malignização nas diversas espécies que infecta, de forma análoga ao tipo humano (Daling , 1992)

d) Coerência, Plausibilidade Biológica e Modelo Experimental:

Estudos *in vitro* reproduzem o modelo biológico de carcinogênese que os estudos epidemiológicos sugerem. Estudos laboratoriais demonstraram que alterações citológicas só ocorrem após a integração do genoma do HPV ao genoma celular da célula epitelial. Antes disso, apesar de poder ser detectada por métodos moleculares, a infecção não produz alterações celulares diagnosticáveis e o genoma do HPV se apresenta na sua forma episssomal (circular, não integrada), o que corresponderia a uma infecção latente. Outros estudos demonstram que os tipos oncogênicos de HPV produzem proteínas E6 e E7 que são fundamentais para a transformação maligna da célula epitelial e o fazem ao se ligar e inativar as proteínas reguladoras do crescimento p53 e Rb. Este processo parece ser o componente central da transformação maligna do câncer cervical (Cannistra et al., 1996).

5. Co-fatores

5.1.Fumo:

Vários estudos demonstraram um risco aumentado de câncer de cérvice associado ao consumo de tabaco. Esta relação poderia significar um fator de confusão com práticas sexuais e conseqüentemente exposição ao HPV. Porém, estudos de coorte e caso-controle em que ambos, casos e controles, eram mulheres HPV-positivas demonstraram que a associação é real e independente (Castellsague e Munoz, 2003 e Brinton et al,1992). O excesso de risco demonstrado nestes estudos (analisados através da razão de chances – OR) é de 2 a 5 vezes quando mulheres com história de exposição ao fumo são comparadas com mulheres que nunca fumaram. Em um estudo recente em que dose-resposta à exposição foi avaliado (Castle et al, 2002), uma associação crescente linear foi demonstrada. Em outro estudo, em que casos de adenocarcinoma de cérvice foram analisados em separado, o risco de desenvolver neoplasia é inversamente relacionado à exposição ao tabaco (Lacey et al. 2001), como para carcinoma de endométrio.

A descrição de metabólitos do tabaco detectáveis em secreção cervical inclusive superiores ao do sangue sugere um efeito carcinogênico direto do tabaco na cérvice uterina (Hellberg et al, 1988).

5.2. Anticoncepcional Oral (ACO)

Recente metanálise publicada em 2003 (Smith et al,2003) conclui que entre mulheres HPV-positivas, uso de anticoncepcional oral aumenta o risco de câncer cervical inclusive com aumento de risco proporcional ao tempo de exposição. Esta associação é positiva e elevada para carcinoma epidermóide e adenocarcinoma, para lesões invasivas e *in situ.* Lacey e colaboradores (1999) descreveram uma associação positiva entre adenocarcinoma de cérvice e uso de anticoncepcional oral que se tornava estatisticamente não-significativa ao ajustar para outros fatores de risco como fumo, idade, número de parceiros sexuais e número de exames de rastreamento nos últimos 10 anos. Após ajustamento, o risco só se manteve elevado para mulheres usuárias de ACO no momento do

estudo para adenoacrcinoma *in situ*. Um estudo de coorte de mulheres infectadas pelo HPV nos EUA não demonstrou associação do uso e ACO e câncer de colo uterino ou lesões de alto grau. Neste estudo, a exposição era aferida apenas na linha de base (Castle et al., 2002). Carcinomas de intervalo (*rapid-onset*) não parecem ter um risco elevado em relação ao uso de ACO (Hildesheim et al, 1999). Os estudos que mais demonstram um excesso de risco são estudos de caso-controle. Porém, deve-se considerar nestes estudos a possibilidade de que práticas de rastreamento e anticoncepção acessadas retrospectivamente podem confundir esta associação .

5.3. Multiparidade

Multiparidade é fator de risco para câncer de colo uterino e suas lesões precursoras só quando o número de nascidos vivos é superior a sete (Castellsague e Munoz, 2003). Na análise que agrupou diversos estudos de caso-controle do IARC um excesso de risco para carcinoma invasivo *ou in situ* foi observado a partir de três gestações a termo e um efeito dose-resposta podia ser observado (Munoz et al, 2002). Neste mesmo estudo, a associação com paridade e adenocarcinoma ou carcinoma adenoescamoso não se mostrou estatisticamente significativa.

O mecanismo de ação deste excesso de risco ainda não é totalmente esclarecido porém hipóteses têm sido formuladas em torno do possível papel das alterações hormonais durante a gestação, alterações na fisiologia da cérvice no período peri-parto, mecanismos imunológicos e inclusive comprometimento nutricional afetando de alguma forma os mecanismos anteriores.

5.4 Nutrientes:

A hipótese de que perfil nutricional esteja associado ao risco de câncer de cérvice e suas lesões precursoras tem interessado os pesquisadores há alguns anos. Porém, a necessidade de se restringir a população em estudo entre mulheres HPV-positiva e as dificuldades metodológicas de se definir grau de exposição a determinados nutrientes faz com que não se tenha uma conclusão definitiva. Os nutrientes mais investigados como tendo um efeito protetor foram

beta-caroteno, licopeno, alfa-carotenóide e vitaminas A, C e E, porém seus resultados nos diversos estudos são inconsistentes (Eichholzer et al, 2001). Inclusive ensaios clínicos de enfoque preventivo (quimioprevenção) com ácido fólico ou beta-caroteno foram feitos, porém todos foram inconclusivos (Alvarez et al., 2003).

5.5. Fatores Hormonais:

Por um longo tempo, características da história gineco-obstétrica da mulher como idade da menarca, idade da menopausa e início das relações sexuais que podiam traduzir uma influência hormonal na patogênese deste tumor foram consideradas fatores de risco para câncer cervical. Após a introdução de teste de HPV nos estudos epidemiológicos que analisavam estas associações, estes fatores não mais se mostraram significativamente associados a esta neoplasia.

Considerando que a cérvice uterina apresenta receptores de estrogênio e progesterona, é lógica a hipótese de que estes hormônios tenham influência na sua carcinogênese. Além disso, apesar de paridade e uso de anticoncepcional oral diminuírem a exposição a níveis de estrogênio endógeno, são fatores de risco quando ocorre uma exposição elevada. Estudos *in vitro* demonstraram um efeito de estrógeno sobre oncogene viral (Auborn et al., 1991). Porém, estudos epidemiológicos falharam em demonstrar um efeito importante desta exposição.

Um estudo avaliou risco de carcinoma epidermóide e adenocarcinoma associado ao uso de terapia de reposição hormonal. Um excesso de risco foi descrito relacionando reposição com estrogênio sem oposição de progesterona com adenocarcinoma de cérvice (Lacey et al 2000). Porém os números eram pequenos. Esta associação não era positiva para carcinoma epidermóide.

5.6. Imunidade

Pacientes imunocomprometidos por infecções do vírus da AIDS ou transplantados têm maior risco de desenvolver lesões precursoras do câncer de cérvice e persistir com infecção por HPV (Palefsky e Holly, 2003). Este risco aumenta quanto mais comprometido está o sistema imune (medido pelos níveis de CD4, por exemplo). O risco de outras neoplasias associadas ao HPV, como

ânus, também está relacionado à imunodepressão. Porém, esta associação para câncer cervical não tem sido consistente nos estudos que avaliaram esta relação.

O mecanismo mais provável deste comprometimento deve estar relacionado à imunidade celular. Talvez pela falta de um marcador de resposta imune à infecção no estágio final da carcinogênese e por a infecção pelo HPV se restringir ao epitélio é que seja difícil demonstrar a associação com câncer de cérvice. No entanto, os resultados atuais demonstram a importância da resposta à infecção pelo HPV para a patogênese do câncer de cérvice.

5.7. Outros Agentes Infecciosos:

Antes de o HPV ser identificado como fator essencial para o câncer de cérvice e suas lesões precursoras, vários agentes sexualmente transmissíveis foram estudados e identificados como associado a esta neoplasia. No entanto, os estudos epidemiológicos mais recentes demonstram que poucos destes agentes estão realmente associados ao câncer de cérvice. O Vírus do Herpes Simples (HSV-2) e a *Chlamydia trachomatis* demonstraram ser co-fatores do câncer de cérvice.

Um estudo que reuniu 7 estudos de caso-controle demonstrou um OR de 1,72 (IC 95% 1,21-2,44) para mulheres HSV-positivas com carcinoma epidermóide e 2,43 (IC 95% 1,22-4,81) para adenocarcinoma e carcinoma adenoescamoso, apos ajustar para outros fatores reconhecidamente associados à exposição a doenças sexualmente transmissíveis e infecção por HPV (Smith et al., 2002a).

Smith e colaboradores (2002b), estudando duas populações diferentes, também encontraram um risco significativamente elevado (OR 2,1) relacionado a detecção de anticorpos por microimunofluorescência para *Chlamydia trachomatis* entre mulheres HPV-positivas.

Como não há evidências de incorporação genética destes agentes ao genoma da célula epitelial, a hipótese mais estudada para explicar este excesso de risco relacionado à exposição a estes agentes é um provável mecanismo de inflamação crônica da cérvice uterina (Castle e Giuliano, 2003)

5.8. História Familiar:

Pouco se sabe sobre a participação do fator hospedeiro na patogênese do câncer de cérvice. A resposta do hospedeiro à infecção por HPV e seu papel na persistência da infecção e conseqüente evolução para neoplasia é uma das variáveis menos conhecidas. Também são pouco estudados o papel da agregação familiar e, principalmente, os diversos aspectos que esta agregação familiar pode representar, como por exemplo, fatores hereditários que possam determinar a resistência à infecção ou a capacidade de eliminá-la, resposta imune à malignização, efeitos do ambiente compartilhado, agrupamento de culturas, hábitos e práticas sexuais.

Alguns estudos relacionando história familiar de câncer e lesões de alto grau ou câncer de cérvice encontraram um excesso de risco entre os indivíduos com história de câncer entre familiares . A maioria destes estudos foi realizada em base populacional nos países escandinavos (Hemminki e Czene, 2002, Hemminki, Li e Mutanen, 2001, Magnusson et al., 2000 e Magnusson, Sparen e Gyllensten,1999). Alguns estudos com gêmeos univitelinos, porém, demonstraram resultados discrepantes para esta associação (Lichtenstein et al., 2000 e Ahlborn et al., 1997). Os resultados não são consistentes, são na sua maioria coortes retrospectivas e não avaliam associação com HPV ou práticas de rastreamento na população estudada.

5.8.1. Genética:

Genericamente, duas classes de susceptibilidade gênica existem: genes com variantes alélicas que conferem alto risco para determinado câncer, os genes de alta penetrância. E os genes que conferem ao indivíduo um risco pequeno a moderado de desenvolver câncer, os genes de baixa penetrância. Estes últimos são variantes de alelos relativamente comuns.

As doenças causadas pelos genes de alta penetrância são raras na população em geral. Por outro lado, os genes de baixa penetrância contribuem para os chamados casos esporádicos, muito mais comuns. Estes casos são, geralmente, o resultado da interação de fatores genéticos e ambientais.

Os genes mais prováveis de estarem envolvidos no risco para câncer de cérvice são os de baixa penetrância e acredita-se que o envolvimento genético desta neoplasia consiste em um grande número de alelos, todos contribuindo com baixo risco. Neste sentido, vários grupos de pesquisa têm descrito polimorfismos gênicos candidatos a estarem relacionados ao risco para câncer de cérvice. No entanto, estudos que envolvam número maior de mulheres ainda são necessários para descrever estes genes.

Resposta a agentes infecciosos também pode ser definida geneticamente. Os estudos mais importantes que implicam uma possível determinação genética da resposta do hospedeiro à infecção são os estudos com genes dos antígenos de histocompatibiliadde (HLA, antígeno leucocitário humano). Estes antígenos são os responsáveis por apresentar ao sistema imune o antígeno de agentes estranhos ao corpo humano, como os vírus. Genes da classe I e II estão sendo estudados e demonstram que alguns alelos são candidatos a estarem relacionados à resposta à infecção pelo HPV (Hildesheim e Wang, 2002). O alelo do HLA da classe II DRB1*13 e os haplótipos contendo este alelo têm sido consistentemente relacionados à diminuição de risco para este câncer (Wang e Hildesheim, 2003).

Outra possibilidade de relacionar o perfil genético do hospedeiro à evolução desta neoplasia é a forma que determinados polimorfismos genéticos, que regulam a resposta imunitária, podem estar associados a outros co-fatores, como a susceptibilidade aos carcinógenos do tabaco. Determinantes genéticos de outras características ou susceptibilidade a outros agressores é que aumentariam o risco de uma mulher a desenvolver este câncer. Porém, os resultados disponíveis ainda são inconclusivos.

Confirmada a influência de fatores genéticos para o desenvolvimento de câncer de cérvice em qualquer uma de suas fases, uma agregação familiar seria observada.

5.8.2. Fatores não-genéticos:

Padrões de cuidados com a saúde são culturalmente influenciados. Logo, práticas preventivas, como rastreamento de câncer de colo uterino, podem se agrupar em família. Além disso, se um familiar é diagnosticado com uma

determinada neoplasia isso pode ser motivo para que familiares próximos aumentem suas práticas de promoção de saúde como rastreamento para câncer o que aumentaria o diagnóstico de lesões pré-neoplásicas neste grupo (Fletcher et al., 1996).

Práticas sexuais também são culturalmente influenciadas, logo, exposição a doenças sexualmente transmissíveis pode se agrupar em núcleos familiares.

Além disso, determinantes sociais do processo saúde-doença,como acesso ao sistema de saúde ou nível educacional, podem se distribuir de forma a afetar familiares de primeiro grau de forma homogênea, influenciando as práticas preventivas e diagnósticas.

Todos estes fatores poderiam de uma forma mais ou menos intensa influenciar o agrupamento familiar deste câncer e mesmo interagir com fatores genéticos, aumentando a agregação familiar.

6. Questões Metodológicas:

Para realizar a presente tese dois artigos originais foram produzidos. No primeiro, uma revisão bibliográfica dos artigos disponíveis sumarizou os achados da associação entre história familiar de câncer e risco para câncer de cérvice.

Os estudos que avaliam a associação entre história familiar de câncer e risco para câncer medem esta associação de formas variadas. Para realizar uma revisão da literatura é importante reconhecer que todos eles de alguma forma estimam risco relativo. Por características dos dados disponíveis ou pela forma que o banco de dados foi organizado, estes estudos usam uma ou outra forma para medir o efeito de história familiar sobre o risco de desenvolver o mesmo câncer (câncer concordante) ou outro câncer (câncer discordante).

As medidas de efeito mais comumente usadas nestes estudos são:

- SIR (standardized incidence ratios): razão de incidências padronizadas, onde a incidência do câncer em indivíduos com história familiar de câncer observada (O) é comparada com a incidência esperada (E - incidência esperada para aqueles sem história familiar de câncer por sítio, sexo e grupo etário).

- FRR (familial relative risk): risco relativo familiar, onde taxas padronizadas por idade de câncer familiar (exposto) são divididas por taxas padronizadas por idade gerais do mesmo câncer (não-exposto).
- Adjusted RR (adjusted relative risk): risco relativo ajustado por coortes de nascimento, onde o risco relativo é calculado pela incidência de câncer nas coortes de nascimento a cada 5 anos entre filhos que tem história familiar de câncer entre os pais (incidência nos expostos) com incidência entre filhos da mesma coorte sem esta história (incidência nos não-expostos).
- OR em estudos de gêmeos (odds ratio): onde pares de gêmeos em que o irmão gêmeo tem história do mesmo câncer (pares concordantes) é comparado com pares de gêmeos em que o irmão gêmeo não tem história de câncer (pares discordantes), para o qual na tabela de contingência para calcular a razão de chances a = ao número de pares de gêmeos concordantes com câncer, b = c = a metade do número de pares discordantes e d = o número de pares concordantes sem câncer.
- RR em estudos de gêmeos (relative risk): onde a incidência de câncer nos pares monozigóticos com o mesmo câncer é dividida pela incidência de câncer nos pares dizigóticos com o mesmo câncer.

Formas menos comuns de medir esta associação também é encontrada, como:

- MRG (median of rates of GIF's): mediana das taxas de medida de agregação familiar (GIF). A mediana observada é calculada através da razão da taxa de agregação familiar de pares de indivíduos com o mesmo câncer (GIF) pela taxa de agregação de 100 pares de indivíduos randomicamente selecionados (controles).
- FHR (familial hazard ratios): modelo de riscos proporcionais familiares, onde o modelo calcula o risco de câncer nos filhos pelo risco de câncer do mesmo tipo nos pais.
- Familial index: índice familiar de câncer, onde o número de parentes em primeiro grau com câncer de uma coorte de indivíduos com um determinado tipo de câncer é dividida pelo número de parentes de primeiro grau com câncer de uma coorte de indivíduos sem câncer.

Também há estudos em que risco relativo, razão de chances e correlações são medidas de forma tradicional.

Para o artigo de análise dos bancos de dados em que a associação de história familiar de câncer estava disponível para avaliar seu efeito sobre o risco para desenvolver câncer de cérvice, tinha-se uma variável de desfecho em 3 níveis. A saber, para o banco de dados do estudo de caso-controle na região leste dos EUA, o desfecho separa-se em câncer epidermóide de cérvice, adenocarcinoma de cérvice e controles. Paro o estudo transversal da Costa Rica, a variável de desfecho tem também 3 níveis, carcinoma epidermóide ou sua lesão precursora neoplasia intra-epitelial 3 (NIC 3), neoplasia intra-epitelial 2 (NIC 2) e mulheres não doentes.

A regressão politômica ou multinomial é o modelo mais indicado para estimar risco de desenvolver um desfecho em mais de 2 categorias, segundo Hosmer e Lemeshow (2000). Ela é particularmente utilizada para a análise de subtipos de doenças, quando não há um ordenamento das categorias da variável dependente. Neste tipo de regressão, ao invés de se criar arbitrariamente variáveis de planejamento (“dummy” variable), todas as categorias da variável de desfecho são analisadas no mesmo modelo. Este método é considerado uma extensão do modelo binário.

Capítulo II - Objetivos

Objetivos

Objetivo Geral:

- Avaliar a associação entre história familiar de câncer e risco para câncer de cérvice

Objetivos Específicos:

- Avaliar a associação entre história familiar de câncer de cérvice, câncer ginecológico e outros cânceres e risco para câncer de cérvice;
- Avaliar a associação entre história de câncer entre mães, irmãs e filhas e risco para câncer de cérvice;
- Avaliar a associação entre história familiar de câncer e risco para câncer de cérvice por tipo histológico.

Capítulo III – ARTIGO I

Family History as a Risk Factor for Cervical Carcinoma: A Review of the Literature

Alice de M. Zelmanowicz, M.D.[1] and Allan Hildesheim, Ph.D.[2]

Affiliations of authors:

[1]Programa de Pós-graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul

[2] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Correspondece to:

Alice de M. Zelmanowicz, M.D., Programa de Pós-graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul

Keywords: cervical carcinoma, family history, and attributable risk fraction

Running title: Family History and Cervical Cancer

ABSTRACT

Family history of cancer has been demonstrated to be associated with increased risk of many types of cancer. Several studies using a variety of study design also showed an elevated risk to cervical cancer. However, the nature of exposition (type of relationship, type of cancer, stage of disease) and the outcome (in situ versus invasive, histological type) can vary too much. The main proposal of this study was to identify all published studies that associate family history of cancer and risk for cervical cancer and summarize the evidences. Twenty studies were located and analyzed in two main groups; concordant cancer and discordant cancers. Approximately, a two-fold excess risk for cervical cancer could be detected. This association is important for *in situ* and invasive cancer. The association of family history of adenocarcinoma of the uterine cervix and risk for squamous cervical cancer is weaker. Studies with individuals with different degree of genetic background could show a dose-response effect. In summary, as in other tumors, family history of cancer is a risk factor to cervical cancer but the fraction attributable to this exposition does not justify the selection of a high-risk group for whom extra screening resource should be offered.

Introduction:

Cervical cancer is one of the most common cancers among women. It was responsible for more than 233.000 deaths worldwide in 2000 (Parkin D.M. et al, 2001), and in many developing countries it is the leading cause of cancer mortality among women.

Infection with oncogenic types of Human Papillomavirus (HPV) is the main cause of cervical cancer (IARC, 1995 e Munoz N. et al, 2003). However, while HPV infection is very common among sexually active women, the vast majority of infections caused by HPV is transient and resolve within one to two years without any sequelae.

In developed nations, early detection through repeated cervical cytology has been effective in lowering incidence and mortality associated with cervical cancer (Jemal A. et al, 2003) However, implementation of such screening programs is expensive (>U$ 5 Billion annually in the US) and require a wide coverage of women over many years to be effective. The high cost associated with such wide coverage, along with the difficulties of setting up high quality cytology collection, handling, and interpretation processes are probably the main obstacles to the implementation of successful cervical cancer screening programs in resource-poor nations. Identification of women at a high-risk of developing cervical cancer could increase the feasibility of establishing successful screening programs in developing nations, by allowing such prevention programs to focus their resources and efforts on subgroups at highest risk of disease.

For this reason, work to define risk factors that are associated with the persistence and progression of common HPV infections to the much rarer pre-cancer lesions and invasive cervical cancer is fundamental.

To date, numerous factors associated with persistence and progression of HPV infection have been identified. These include viral factors, e.g., HPV type variants (Wang S.S. and Hildesheim A. 2003), lifestyle factors, e.g., parity, smoking and oral contraceptive use (Hildesheim A, et al. 2001.; Munoz N. et al. 2002, Smith J.S. et al., 2003), and host factors, e.g., immune response to HPV and genetic susceptibility (Wang S.S. and Hildesheim A. 2003, Magnusson,P.K., Sparen,P. and

Gyllensten,U.B. 1999). Family history of cervical and other cancers, which could be an indicator of either genetic susceptibility and/or shared environment between related individuals, has also been suggested to be a risk factor for cervical cancer.

The purpose of this report is to identify all published studies between 1980 and 2003 that have analyzed the association between *in situ* or invasive cervical cancer and family history of cervical or other cancers, and to summarize the evidence from these studies to determine 1) whether there is consistent evidence for familial aggregation of cervical cancer, and if so 2) whether targeting prevention services to women with a positive family history might be a useful strategy for the control of cervical cancer in resource-poor countries.

Methods:

Search Methods:

Published studies were identified using the MEDLINE database, from 1980 to 2003.

The search terms used were: family history and cancer, familial risk and cancer, familial cancer, familial tumor, heritability of cancer, cancer in parents, cancer in offspring, familiality of cancer, cancer in relatives, risk factor and cervical cancer or uterine cervix cancer.

Studies where the association between family history of any cancer and risk of cervical cancer was evaluated were selected for review.

Additional searches in MEDLINE were performed to identify studies that utilized specific large registry databases, including The Swedish Family-Cancer Database, the Utah Population Database and Nordic Twin Registries.

Finally, to supplement these searches, the reference lists of articles identified through MEDLINE searches defined above were reviewed to identify additional articles that might fit the inclusion criteria.

Unpublished material was not assessed.

Review of selected articles**:**

Any measure of association that reflects risk was extracted by one of the authors (AMZ). Information on population, study sample, sample size, design and main measure of association were also collected. Authors use several different measures of effects to estimate risk. To know, the most common were: SIR, standardized incidence ratios, where incidence of cervical cancer with family history observed was compared with incidence expected (incidence expected for those lacking a family history of cancer by site, sex and age group); FRR, familial relative risks, where age-specific rates for familial cancer were divided by all cancers at the same site rates; adjusted RR, birth cohort-adjusted rates, where relative risk were calculated using 5-years cohort-specific rate for offspring by parent cancer history; OR (odds ratio) for twin studies, where those with and those without cancer in twin partner, estimated as ad/bc with a = the number of concordant pair with same site cancer, b = c = one half the number of discordant pairs and d = the number of concordant pairs without cancer. RR, risk relative in twin studies, estimates as the incidence rate in monozygotic dived by incidence rate in dizygotic among twins with same site cancer in partner. There were also traditional relative risk for cohort studies, traditional odds ratio for case-control studies and tetrachoric correlations, R. Measure of effect less common were also used as MRG, median of rates of GIF. This median is a measure of how the degree of family clustering (GIF) observed varies in relation to expected. They calculate the median of the distribution of the ratio of the case GIF to the 100 control GIFs for a specific cancer site. FHR, familial hazard ratios, where using logistic regression model they calculate risk for cancer in offspring, by concordant for parental cancer. Familial index is the number of first-degree relatives with cancer of a cohort of individuals with cancer divided by the number in the control cohort.

Data on familial history of cervical cancer as a risk factor for cancers other than cervical cancer were not included in this review, since we focused our efforts on studies that evaluated cervical cancer as the outcome of interest. Case reports and case series were also excluded.

Since the study designs and the methodological approaches used to evaluate familial risk varied considerably between studies, no attempt was made to pool data

across studies. Instead, results from individual studies were summarized in table format.

Results:

Twenty articles were identified that evaluated risk of cervical cancer associated with family history of cancer. Studies that evaluated risk of cervical cancer associated with a family history of cervical cancer (concordant cancer studies summarized in Tables 1 and 2) and those that evaluated risk of cervical cancer associated with a family history of cancers other than cervical cancer (discordant cancer studies summarized in Table 3) were reviewed separately. When reviewing the concordant cancer studies, we further evaluated studies that reported on *in situ* cervical cancer as the outcome of interest (Table 1) and those that reported on invasive cervical cancer as the outcome of interest (Table 2) separately. Studies that combined *in situ* and invasive cases were reviewed with the studies of *in situ* cervical cancer, since these studies are likely to be heavily weighted towards *in situ* cervical cancer outcomes, given that *in situ* cervical cancer is a much more common diagnosis than invasive cervical cancer.

Concordant Cancer Studies:

Risk for *In Situ* Cervical Cancer:

Seven studies evaluated the risk of *in situ* cervical cancer among women with a family history of cervical cancer. These studies are summarized in table 1.

Six of the seven studies that evaluated risk of *in situ* cervical cancer by family history of cervical cancer are from Sweden. These studies relied on one of two large databases, based on The Swedish Family-Cancer database and the Swedish Twin Registry. The Swedish Family-Cancer database has information on all persons born in Sweden after 1931 along with information on their biological parents. Information on cancers reported to the nationwide Swedish cancer registry starting in 1958 is also included in this large database. The database currently contains information on over 10 million individuals from over 3 million families. The Swedish Twin Registry is a nationwide registry that contains information on same-sex twins since the end of

the eighteen-century. It consists of two cohorts: the old and the young cohort. The old cohort contains information of all same-sex twins born during the period of 1886-1925 with both individual alive when the registry was established in 1959-61. At that time, twins were asked to answer a questionnaire. Information of 10 503 pairs could be assessed. The young cohort included all twins born during the period of 1926-1958 who were alive in 1970. They answered a questionnaire in 1972 and information of 12 883 pairs is available. These two cohorts were linked to the Swedish Cancer Registry. They use a retrospective cohort design to analyze the association with some different measures of association.

Results from the six studies from Sweden (Ahlbom A. et al. 1997, Hemminki K et al. 1998a, 1999a, 2001; Magnusson, P.K., 1999 and 2000) consistently reported elevations in risk of *in situ* cervical cancer associated with a family history of cervical cancer. The risk estimates reported in these studies ranged from 1.4 for having a daughter with invasive cancer in the study by Hemminki K et al. (1999a) to 4.8 in the study by Ahlbom and colleagues in which risk of disease among monozygotic and dizygotic twins were evaluated (Ahlbom A. et al. 1997). In this latter study, only the young cohort was analyzed to minimize screening biases, risk among monozygotic twins was 4.8-fold that observed in monozygotic partner with no cancer history while it was found to be 2.0-fold when monozygotic twins were compared to dizygotic twins, suggesting that this residual 2-fold excess in risk is likely to be due to genetic risk factors rather than shared environment.

Elevations in risk were seen regardless of whether maternal history, history among sisters, or history among daughters was examined. Furthermore, stage of disease (*in situ* versus invasive) among the relative with a history of cervical cancer did not appear to affect the magnitude of risk observed. The one exception to the studies that observed increased risk associated with family history comes from the single study that was able to evaluate risk of *in situ* squamous cell cervical carcinomas by family history of squamous and glandular tumors separately. Although based on small numbers, this study by Hemminki and colleagues (Hemminki K, et al, 2001) found no evidence for an association between a maternal history of *in situ* adenocarcinoma and risk of *in situ* squamous cell carcinoma (SIR = 0,91). However, in this same study elevations in risk of *in situ* squamous cell carcinoma were observed for a maternal history of invasive adenocarcinomas (SIR = 1,43, 95% CI 1,14-1,75), and for a history of in situ (SIR = 1,73, 95% CI 0,98-2,67) or

invasive (SIR = 1,25, 95% CI 0,76-1,85) adenocarcinoma among daughters. Exception is the association between history of *in situ* Adenocarcinoma of uterine cervix among mothers that did not show statistically significance (SIR = 0,91).

Control for confounding variables was not possible in any of the record linkage studies summarized above, making it difficult to determine whether associations noted with family history reflect true genetic susceptibility to cervical cancer or shared environmental and/or lifestyle factors among relatives. Most importantly, HPV infection status was not assessed in any of the record linkage studies, and screening practices were not evaluated as potential explanatory factors for the observed family history association. However, in one study by Magnusson and colleagues (1999) the association between family history of cervical cancer and risk of *in situ* or invasive (>85% of cases were *in situ*) cervical cancer was assessed separately for biological and non-biological relatives, in an attempt to evaluate whether the familial association reported in previous studies was due to non-genetic factors (in which case elevations in risk would be expected for biological and non-biological relatives) or to true genetic predisposition (in which case elevations would be expected to be observed for biological relatives only). Results from this study indicated that risk associated with family history of cervical cancer was strongest when the relative with cervical cancer was a biological mother (RR = 1,83) or a biological full sister (RR = 1,93), intermediate when the relative with cervical cancer was a half-sister (RR = 1,45), and weakest when the relative with cervical cancer was either an adoptive mother (RR = 1,10) or a non-biological (i.e., adopted) sister (RR = 1,15).

In addition to the Swedish record linkage studies discussed above, one case-control study reported by Furgyik and colleagues (Furgyik S. at al., 1986) evaluated the association between a family history of cervical cancer and risk of *in situ* cervical cancer. In this study, which included patients hospitalized at the department of Gynecology in Malmo, Sweden, and their male consorts as controls, a positive association was observed between a family history of cervical cancer among sisters and/or mothers and *in situ* cervical cancer.

Risk for Invasive Cervical Cancer:

Thirteen studies evaluated the risk of invasive cervical cancer among women with a family history of cervical cancer. These studies are summarized in table 2.

As was the case for studies that evaluated *in situ* cervical cancer as an outcome, many of the studies that evaluated invasive cervical cancer as the outcome of interest were conducted in Sweden and utilized data from The Swedish Family-Cancer database (Ahlbom A. et al. 1997, Hemminki K et al. 1998a, 1998b, 1999a, 2001 and 2002; Linchtenstein P. et al. 2000; Dong C. et al. 2001 and Lindelof B et al., 2001). Results from these Swedish record linkage studies consistently reported elevations in risk of invasive cervical cancer associated with a family history of cervical cancer. The risk estimates reported in these studies ranged from 1.7 in the study by Hemminki and colleagues where Familial Relative Risks (FRR) were estimated for family history of *in situ* of any cancer as expose (Hemminki K. et al., 1998) to 4.5 in the study by Hemminki in 1999 (Hemminki K et al., 1999a) where having more than one daughter with *in situ* cervical cancer was particularly associated to risk for invasive cervical cancer.

Elevations in risk were seen regardless of whether maternal history, history among sisters, or history among daughters was examined. Furthermore, stage of disease *(in situ* versus invasive) among the relative with a history of cervical cancer did not appear to affect the magnitude of risk observed. The single study that was able to evaluate risk of invasive squamous cell cervical carcinomas by family history of squamous and glandular tumors separately consistently observed an association with invasive cervical cancer of both maternal (SIR = 1,46, 95% CI 0,38-3,25) and daughter (SIR = 1,53, 95% CI 0,73-2,63) history of invasive cervical adenocarcinoma, although this association was weaker than that observed for familial history of squamous cell cervical cancer and not statistically significant due to the small number of cases with a history of cervical adenocarcinoma.

In addition to the record linkage studies conducted in Sweden, two twin-based studies that evaluated invasive cervical cancer as the outcome of interest were conducted in Scandinavia, one in Finland (Verkasalo PK et al. 1999) and the second study combining databases from Denmark, Finland, and Sweden (Lichtenstein P et al., 2000). In contrast to the twin-based study of *in situ* cervical cancer conducted in Sweden, no excess risk of disease was associated with monozygosity in either of these two reports. In fact, in the study by Lichtenstein and colleagues excess risk of invasive cervical cancer was observed among dizygotic twins compared to monozygotic twins. The authors of this report concluded that shared environmental factors accounted for an estimated 20% of invasive cervical cancer cases among

twins, non-shared environmental factors accounted for an estimated 80% of cases, while heritable factors did not contribute to the development of invasive cervical cancer among the twin pairs studied. It should be noted that limitations of these twin-registry studies include survivor as twins needed to be alive to answered a questionnaire when the twin registry was established and the fact that zygozity was assessed through interviews only.

Two record linkage studies of invasive cervical cancer were reported from studies in the United States (Cannon-Albright LA et al., 1994 and Goldgar DE et al., 1994). Both of these studies utilized data from the Utah Population Database. This registry contains birth, death, geographical and marriage information on over one million Utah Mormon pioneers and their descendents since 1894. This genealogical database was linked to the statewide Utah Cancer Registry, a registry established in 1952, to permit an analysis of the association between cervical cancer family history and risk of invasive cervical cancer.

Using different statistical approaches, both studies reported an association of invasive cervical cancer with a family history of cervical cancer. In the study by Cannon-Albright and colleagues significant excess in familial clustering was observed among invasive cervical cancer cases compared to non-. In the parallel study by Goldgar and colleagues, evidence for an elevated familial RR was observed (FRR = 1,74), although this elevation did not reach statistical significance. Taken together, these two studies lend support for an association between family history and invasive cervical cancer. Limitations of the Utah studies include potential lack of generalizability of data obtained from a relatively homogeneous Utah Mormon population to the more heterogeneous US population, and any biases that might have arisen due to lack of complete information on mortality and migration among relatives of cervical cancer cases in the database.

In addition to the record linkage studies summarized above, two case-controls studies conducted in separate populations evaluated the risk of invasive cervical cancer associated with family history. Brinton LA. et al. reported results from a multicenter case-control study of cervical cancer in the US in which squamous and glandular tumors were evaluated separately. They reported statistically significant univariate associations between family history of cervical cancer and Adenosquamous (OR = 9.9) and squamous cell carcinoma (OR = 3.1) of the cervix.

After control for potential confounding by screening practices and other questionnaire-based risk factors only the association with adenosquamous carcinomas remained statistically significant (OR = 12). An elevation in risk was also observed in univariate analysis for adenocarcinomas (OR = 2.5), but this effect did not reach statistical significance due to the small number of cases. Finally, in a hospital-based case-control study from Korea reported by Yoo KY et al. (1997), family history of cervical cancer was associated with a 2-fold excess risk of invasive cervical cancer. In their report, the authors suggest that the study was not prone to recall bias since the interviews was performed before diagnosis for both cases and controls. No HPV status was assessed. With the exception of the two case-control studies, which adjusted for screening behavior and other risk factors for cervical cancer (with the notable exception of HPV), control for confounding variables was not possible in any of the record linkage studies summarized above, making it difficult to determine whether associations noted with family history reflect true genetic susceptibility to cervical cancer or shared environmental and/or lifestyle factors among relatives. Most importantly, HPV infection status was not assessed in any of the studies, and screening practices were not evaluated as potential explanatory factors for the observed family history association in the record linkage studies.

Discordant Family History:

The six studies we identified that evaluated the risk of *in situ* or invasive cervical cancer associated with a family history of cancers other than cervical cancer (discordant cancers) are summarized in table. All but one of the studies were conducted in Sweden using resources from The Swedish Family-Cancer Database. The single study conducted outside of Sweden was conducted in Utah using the Utah Population Database. Increases in risk associated with a family history of discordant cancers reported in these studies were by en-large in the range of 1.5 to 2.0. Increases were observed with a family history of other cancers known to be associated with HPV infection (oral and anal cancers) or with smoking (lung, bladder, colon, and rectum cancers), both established risk factors for cervical cancer. A family history of liver cancer, lymphoma, ovarian cancer, prostate cancer, and skin cancer was also found to be associated with cervical cancer risk in at least one of these studies.

In addition to the studies summarized in tables 1-3, a few miscellaneous studies have evaluated the role of family history in the development of cervical cancer but could not be included in tables 1-3 since they did not fit the criteria established for those tables.

Risk factors for female genital tract cancer were investigated in an Italian case-control study (Cusimano R. et al., 1989) and an OR of 2,31 was reported for family history; the nature of the family history, however, is not clearly stated in this report.

Hildesheim and colleagues (Hildesheim A et al., 1999) studied risk factors associated to the development of rapid-onset cervical cancer in a US population-based case-control study. Among the non-viral factors linked to this cancer presentation, they found non-significant 70% increase in the risk of development of rapid-onset cancer among cases with a positive maternal history of cervical cancer (95% confidence interval 0, 41-6,8). As all 3 women with positive family history were younger then 40 years old, restricted analysis for this age group reveal a 7,1-fold increased risk of rapid-onset disease (95% confidence interval 1,0-49). Authors concluded that this result could add support to host factors involved in the pathogenesis of cervical cancer.

Discussion*:*

It has been recognized for some time that cancer aggregates in families and that first-degree relatives of cancer cases are at increased risk of same site or discordant site cancers. For most common cancers, a 2- to 3-fold increase in risk of disease has been observed for individuals with a positive family history compared to general population rates (Peto J. and Houlston RS, 2001). Less clear is whether risk associated with family history of cancer is due to an underlying genetic susceptibility to cancer or to shared environmental and/or cultural influences (Risch N., 2001).

Several known hereditary syndromes exist in which excesses in neoplasia are observed. Breast, colon, ovary cancer and melanoma are some of the tumors associated with specific, inherited genetic alterations (Peto J and Houlston RS, 2001, Grann VR and Jacobson JS, 2002). However, while hereditary cancers associated with specific, known genetic alterations do exist, these cancers are rare and account for only a small fraction of all cancers; sporadic tumors appear to account for >95% of cancers diagnosed worldwide (Risch N. 2001).

Cervical cancer has also been reported to aggregate in families. To evaluate available, published evidence on the association between family history of cancer and risk of cervical cancer, we conducted the present review of the literature. As summarized in tables 1-3, the bulk of the evidence from available studies, most of which are record linkage studies conducted in Scandinavia and the United States, suggest that individuals with a family history of cervical cancer among first degree relatives are at a 1.5- to 2-fold increased risk of cervical cancer. This finding appears to be consistent regardless of whether *in situ* or invasive cervical cancer was evaluated as the main outcome of interest, and was also observed regardless of the specific relationship of the family member with a history of cancer (i.e. mothers, sisters, or daughters). Similar results were also observed regardless of study methods used in the design and/or analysis of the various studies.

While results from the studies to date provide consistent evidence that cervical cancer aggregates within families, it is less clear whether this aggregation is due to true underlying genetic susceptibility and/or to shared environmental/lifestyle factors. Of note, none of the studies to date have accounted for HPV infection in cases and their relatives, and the few studies that attempted to control for potential confounding by cervical cancer screening practices or other sexual/behavioral factors were case-control studies likely to be plagued by problems related to differential family history recall among cases and controls. As HPV infection is the main cause of this cancer and behavioral factors that correlate with risk of exposure to HPV can co-segregate in families, evidence for familial aggregation reported in studies to date could be a reflection of shared sexual and behavioral factors that predispose to HPV exposure. Similarly, since risk factors other than HPV itself are likely important determinants of the small fraction of women infected with HPV who progress to cancer, correlation within families of risk factors that might be determinants of persistent infection and progression to cancer (such as parity, oral contraceptive use, and smoking) might also partially explain familial aggregation observed for cervical cancer.

Control for screening practices in studies that assess familial aggregation of cervical cancer is of particular importance, since it is very likely that cervical cancer screening behavior correlates within family members. If an individual within a family is diagnosed with cancer, for example, it is not uncommon for relatives to seek medical attention and for these family members to more actively comply with screening recommendations. Also, health seeking behavior and awareness of

healthy behaviors/lifestyles is known to correlate with socio-economic status and therefore likely to correlate within families. These biases are likely to be attenuated in populations where nationwide cervical cancer screening programs have achieved broad and effective coverage, and so the fact that evidence for familial aggregations was observed in Scandinavian countries where such effective programs are in place suggest that the observed familial effect might reflect at least in part a true underlying genetic susceptibility to cervical cancer.

Additional support for a true genetic effect underlying the observed familial aggregation comes from the studies conducted by Magnusson et al (1999 and 2000) in which the elevation in risk of cervical cancer was greatest for full-blooded relatives, intermediate for half-blooded relatives, and largely non-existent for non-biological relatives. Unless level of blood relatedness is found to co-segregate with environmental or lifestyle factors associated with cervical cancer, the observation in the studies by Magnusson et al. that elevations in risk are only observed for blood-related relatives suggest a true genetic component to the observed familial aggregation observed for cervical cancer. The interpretation that true genetic susceptibility explains the observed familial aggregation seen for cervical cancer is also consistent with results from studies that have directly demonstrated an association between inherited genetic factors and cervical cancer risk (Lynch HT et al, 1998). In this respect, it is of note that specific human leukocyte antigen (HLA) alleles and haplotypes have consistently been observed to be associated with risk of cervical cancer (Wang SS. et al., 2001)

In additional to the results suggesting an association with cervical cancer of a family history of cervical cancer itself, results from the few studies that have evaluated risk associated with a history of cancers other than cervical cancer suggest the possibility that history of cancers other than cervical cancer might also be associated with cervical cancer risk. If true, these findings likely reflect shared exogenous risk factors for these discordant tumors, since many of the discordant cancers whose family history was associated with the development of cervical cancer are known to be associated with either HPV infection (anus and oral) or smoking (lung, oral, bladder, colon, and rectum). Nonetheless, the possibility of common underlying genetic factors that predispose to various cancers, including cervical cancer cannot be ruled out.

Limitations of the present review should be mentioned. First, publication bias is always a concern when literature reviews are performed. To the extent that negative studies exist which were not published, or that were published in Journals not captured within MEDLINE, our review would not have captured those studies. Secondly, this review is limited by its inability to perform a meta-analysis. The study designs and statistical methods employed in the various published studies varied widely, precluding this more formal approach to our review.

Preventive efforts should be focus on those women highly prone to develop cervical cancer, as HPV infection and cytology alteration are so prevalent. To select those who would be most benefit and the preventive procedure would be most cost-effective identification of his thigh-risk group is important. Attributable risk fraction identify the proportion of the cases that can be prevented if the particularly risk factor can be managed. Population attributable fraction of familial risk to a specific cancer is the proportion of a cancer risk related to a familial clustering. If this fraction is high, individual of these high risk families would be a good target to preventive measure as screening.

As far as it could be located through Medline, only one population-based study calculated population attributable fraction of familial risk for cervical cancer. Hemminki and Czene in the more recent up-to-date analyzes of the Swedish Family–Cancer Database (Hemminki K. and Czene K., 2002), describe the attributable risk of familial cancer for several different cancer previously reported. Only 0,93% of the risk for cervical cancer can be attributable for having a mother with cervical cancer history and 0,57% for a history among daughters, considering a risk of approximately two-fold.

Consequently, besides there is a true family history association to cervical cancer, cancer family history as a risk co-factor cannot translate in practical approach to select high-risk women who screening efforts should be implemented.

In conclusion, family history of cervical cancer is a co-factor to cervical cancer, *in situ* or invasive. This association is consistently with any first-degree relative, with exception to twins. For this very special group, studies where greater number of concordant pairs would be very important to clarify the discrepancy found in the studies analyzed in this review. This association is mainly related to squamous cell carcinomas of the uterine cervix. Family history of other cancers associated to risk for cervical cancer is mostly related to tobacco exposition (lung, oral and bladder

cancer) or virus-mediated cancers (liver and anus cancer). As the results are largely based in the Swedish population it would be essential to study this association in other populations.

Family history has consistently been shown to be associated with risk of cervical cancer, although not conclusive, evidence suggests the likelihood that at least some of this association is due to a true genetic susceptibility component to this disease, and whether this underlying genetic susceptibility is an important determinant of risk of infection, persistence, or progression to cancer is still not known and should be the focus of future research.

Reference List

1. Ahlbom, A., Lichtenstein, P., Malmstrom, H., Feychting, M., Hemminki, K., and Pedersen, N. L.Cancer in twins: genetic and nongenetic familial risk factors. J.Natl.Cancer Inst. 1997; 89:287-293.
2. Brinton, L. A., Tashima, K. T., Lehman, H. F., Levine, R. S., Mallin, K., Savitz, D. A., Stolley, P. D., and Fraumeni, J. F., J Epidemiology of cervical cancer by cell type. Cancer Res. 1987; 47:1706-1711.
3. Cannon-Albright, L. A., Thomas, A., Goldgar, D. E., Gholami, K., Rowe, K., Jacobsen, M., McWhorter, W. P., and Skolnick, M. H.Familiality of cancer in Utah. Cancer Res. 1994; 54:2378-2385.
4. Cusimano, R., Dardanoni, G., Dardanoni, L., La Rosa, M., Pavone, G., Tumino, R., and Gafa, L.Risk factors of female cancers in Ragusa population (Sicily)--1. Endometrium and cervix uteri cancers. Eur.J.Epidemiol. 1989; 5:363-371.
5. Dong, C. and Hemminki, K.Modification of cancer risks in offspring by sibling and parental cancers from 2,112,616 nuclear families. Int.J.Cancer 2001; 92:144-150.
6. Furgyik, S., Grubb, R., Kullander, S., Sandahl, B., Wingerup, L., and Eydal, A.Familial occurrence of cervical cancer, stages 0-IV. Acta Obstet.Gynecol.Scand. 1986; 65:223-227.
7. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst. 1994; 86(21): 1600-8

8. Grann V.R. and Jacobson J.S. Population screening for cancer-related germline gene mutations. 2002; 3(6): 341-8
9. Hemminki, K. and Vaittinen, P.Effect of paternal and maternal cancer on cancer in the offspring: a population-based study. Cancer Epidemiol.Biomarkers Prev. 1997; 6:993-997.
10. Hemminki, K. and Vaittinen, P.Familial risks in in situ cancers from the Family-Cancer Database. Cancer Epidemiol.Biomarkers Prev. 1998; 7:865-868.
11. Hemminki, K., Vaittinen, P., and Kyyronen, P.Age-specific familial risks in common cancers of the offspring. Int.J.Cancer 1998; 78:172-175.
12. Hemminki, K., Dong, C., and Vaittinen, P.Familial risks in cervical cancer: is there a hereditary component? Int.J.Cancer 1999a; 82:775-781.
13. Hemminki, K. and Vaittinen, P.Familial cancers in a nationwide family cancer database: age distribution and prevalence. Eur.J.Cancer 1999b; 35:1109-1117.
14. Hemminki, K., Li, X., and Mutanen, P.Familial risks in invasive and in situ cervical cancer by histological type. Eur.J.Cancer Prev. 2001; 10:83-89.
15. Hemminki, K. and Czene, K.Attributable risks of familial cancer from the Family-Cancer Database. Cancer Epidemiol.Biomarkers Prev. 2002; 11:1638-1644.
16. Hildesheim, A., Herrero, R., Castle, P. E., Wacholder, S., Bratti, M. C., Sherman, M. E., Lorincz, A. T., Burk, R. D., Morales, J., Rodriguez, A. C., Helgesen, K., Alfaro, M., Hutchinson, M., Balmaceda, I., Greenberg, M., and Schiffman, M.HPV co-factors related to the development of cervical cancer: results from a population-based study in Costa Rica. Br.J.Cancer 2001; 84:1219-1226.
17. Hildesheim, A. and Wang, S. S.Host and viral genetics and risk of cervical cancer: a review. Virus Res. 2002; 89:229-240.
18. International Agency for Rsearch on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans. Human papillomaviruses. IARC monographs on the evaluation of carcinogenic risks to humans. Vol.64.Lyon (France): IARC; 1995
19. Jemal, A., Murray, T., Samuels, A., Ghafoor, A., Ward, E., and Thun, M. J.Cancer statistics, 2003. CA Cancer J.Clin. 2003; 53:5-26.

20. Lichtenstein,P. et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N. Engl. J. Med. 2000; 343, 78-85
21. Lindelof, B. and Eklund, G. Analysis of hereditary component of cancer by use of a familial index by site. Lancet 2001; 358:1696-1698.
22. Magnusson, P. K., Sparen, P., and Gyllensten, U. B.Genetic link to cervical tumours. Nature 1999; 400:29-30.
23. Magnusson, P. K., Lichtenstein, P., and Gyllensten, U. B.Heritability of cervical tumours. Int.J.Cancer 2000; 88:698-701.
24. Munoz, N., Franceschi, S., Bosetti, C., Moreno, V., Herrero, R., Smith, J. S., Shah, K. V., Meijer, C. J., and Bosch, F. X.Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet 2002; 359:1093-1101.
25. Munoz, N., Bosch, F. X., de Sanjose, S., Herrero, R., Castellsague, X., Shah, K. V., Snijders, P. J., and Meijer, C. J.Epidemiologic classification of human papillomavirus types associated with cervical cancer. N.Engl.J.Med. 2003; 348:518-527.
26. Peto, J. and Houlston, R. S.Genetics and the common cancers. Eur.J.Cancer 2001; 37 Suppl 8:S88-S96.
27. Risch, N. The genetic epidemiology of cancer: interpreting family and twin studies and their implications for molecular genetic approaches. Cancer Epidemiol.Biomarkers Prev. 2001; 10:733-741.
28. Smith, J. S., Green, J., Berrington, de Gonzalez, Appleby, P., Peto, J., Plummer, M., Franceschi, S., and Beral, V.Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet 2003; 361:1159-1167.
29. Verkasalo, P. K., Kaprio, J., Koskenvuo, M., and Pukkala, E.Genetic predisposition, environment and cancer incidence: a nationwide twin study in Finland, 1976-1995. Int.J.Cancer 1999; 83:743-749.
30. Wang, S.S., Wheeler, C.M., Hildesheim, A. et al. Human Leukocyte Antigen Class I and II Alleles and Risk of cervical Neoplasia: Results from a Population-based Study in Costa Rica. J Infect Dis. 2001; 184:1310-14

31. Wang, S. S. and Hildesheim, A. Chapter 5: Viral and host factors in human papillomavirus persistence and progression. J.Natl.Cancer Inst.Monogr 2003;35-40.
32. Yoo, K. Y., Kang, D., Koo, H. W., Park, S. K., Kim, D. H., Park, N. H., Song, Y. S., Kang, S. B., and Lee, H. P. Risk factors associated with uterine cervical cancer in Korea: a case-control study with special reference to sexual behavior. J.Epidemiol. 1997; 7:117-123.

Table 1. Risk of ***In Situ*** Cervical Cancer Associated to Family History of Cervical Cancer (concordant cancer site)

Author (year)	Relative with cervical cancer	Effect	p-value or 95% confidence interval	number of events
Scandinavian Record Linkage Studies				
1. Ahlbom A et al (1997)	Twins (young cohort only)	OR MZ 4,8	3,0-7,6	27 MZ pairs
		OR DZ 2,4	1,5-3,8	22 DZ pairs
		OR MZ/DZ - 2,0	1,1-3,5	
2. Hemminki K. et al. (1998a)	Mother in situ	FRR 1,8	1,7-1,8	2855
	Mother invasive	FRR 1,6	1,5-1,7	942
		age-adjusted FRR		
3. Hemminki K. et al. (1999a)	Mother in situ	1,69	1,64-1,75	2830
	Mother invasive	1,64	1,57-1,70	935
	one daughter in situ	1,92	1,85-2,86	2583
	more than one daughter in situ	2,35	1,84-2,86	124
	Daughter invasive	1,45	1,18-1,72	109
4. Magnusson PK. et al. (1999)	Biological mothers	RR 1,83	1,77-1,88	
(5% invasive)	Adoptive mothers	RR 1,10	0,76-1,54	
	Biological full sisters	RR 1,93	1,85-2,01	not stated
	non-biological sisters	RR 1,15	0,82-1,57	
	Half-sisters	RR 1,45	1,31-1,60	
5. Magnusson PK. et al. (2000)	*old-cohort*			Number of concordant pairs
	Full sister	R 0,15	0,14-0,17	1385
	half-sister (mother)	R 0,11	0,04-0,17	84
	half-sister (father)	R 0,08	0,01-0,14	80
	non-biological sister	R 0,02	-0,12-0,16	17
	mother/daughter	R 0,13	0,12-0,14	2270
	adoptive mother/daughter	R -0,02	-0,13-0,10	16
	young cohort			
	full sister	R 0,17	0,14-0,19	304
	half-sister (mother)	R 0,12	0,04-0,20	31
	half-sister (father)	R 0,05	0,03-0,13	22
	non-biological sister	R 0,15	0,01-0,30	9
	mother/daughter	R 0,14	0,13-0,15	1857
	Adoptive mother/daughter	R 0,05	-0,06-0,16	12

Author (year)	Relative with cervical cancer	Effect	p-value or 95% confidence interval	number of events
6. Hemminki et al. (2001)	Mother, any invasive	SIR 1,52	1,44-1,61	1173
	Mother, invasive SCC	SIR 1,52	1,42-1,61	1040
	Mother, *in situ* SCC	SIR 1,92	1,86-1,99	3305
	Mother, Adeno	SIR 1,43	1,14-1,75	84
	Mother, *in situ* Adeno	SIR 0,91	0,29-1,89	5
	Daughter, any invasive	SIR 1,09	0,92-1,27	145
	Daughter, invasive SCC	SIR 1,57	1,30-1,87	119
	Daughter, *in situ* SCC	SIR 1,66	1,60-1,72	2978
	Daughter, Adeno	SIR 1,25	0,76-1,85	20
	2 or more daughter, *in situ* SCC	SIR 2,61	2,22-3,03	158
	Daughter, *in situ* Adeno	SIR 1,73	0,98-2,67	16
Other Studies				
7. Furgyik S.et al. (1986)	Mother (9% invasive)	7,9% cases X 1,0% controls	<0,01	14 cases in 177
	Sister (14% invasive)	7,5% cases X 1,1% controls	<0,01	14 cases in 188

Table 2. Risk of **Invasive** Cervical Cancer Associated to Family History of Cervical Cancer (concordant cancer site)

Author (year)	Relative with cervical cancer	Effect	p-value or 95% confidence interval	number of events
Scandinavian Record Linkage Studies				
1. Hemminki K. et al. (1998a)	Mother in situ	FRR 1,7	1,4-2,0	127
2. Hemminki K. et al. (1998b)	Mother	FHR 2,0	1,5-2,6	67
3. Hemminki K. et al. (1999a)		age-adjusted FRR		
	Mother, *in situ*	1,66	1,43-1,88	127
	Mother, invasive	2,06	1,70-2,43	67
	Daughter, invasive	3,91	2,95-4,87	61
	one daughter, *in situ*	2,22	2,09-2,35	829
	more than one daughter, *in situ*	4,54	3,46-5,61	51
4.Verkasalo et. Al. (1999)	Twins	SIR MZ 1,10	0,44-2,27	7 MZ
		SIR DZ 1,06	0,58-1,78	14 DZ
5. Linchtenstein P. et al (2000)	Twins	OR MZ 2,9	0,40-21,4	107 MZ
		OR DZ 4,5	1,4-14,4	201 DZ
6. Dong C. et al. (2001)	Offspring	SIR 1,93	1,52-2,42	76
	Sibling	SIR 2,39	1,59-3,46	28

Author (year)	Relative with cervical cancer	Effect	p-value or 95% confidence interval	number of events
7. Hemminki et al. (2001)	Mother, any invasive	SIR 1,87	1,46-2,33	71
	Mother invasive SCC	SIR 1,97	1,52-2,47	67
	Mother *in situ* SCC	SIR 1,84	1,52-2,18	121
	Mother Adeno	SIR 1,46	0,38-3,25	4
	Daughter, any invasive	SIR 2,10	1,66-2,58	80
	Daughter, invasive SCC	SIR 2,24	1,74-2,81	67
	Daughter, *in situ* SCC	SIR 1,64	1,53-1,74	916
	Daughter, Adeno	SIR 1,53	0,73-2,63	10
	2 or more daughter, *in situ* SCC	SIR 2,62	1,99-3,33	59
8. Lindelof B. et al (2001)	first-degree relative	familial index = 1,7	1,3-2,4	239
9. Hemminki K et al. (2002)	Mother	SIR 1,95	1,55-2,40	92
	Sibling	SIR 2,15	1,43-3,02	30
US Record Linkage Studies				
10. Cannon-Albright LA.et al. (1994)	Any	MRG 1,17	0,022	1031
11.Goldgar DE et al. (1994)	First-degree relative	FRR 1.74	0.86-2.91	999
Other Studies				
12. Brinton LA et al. (1987)	First-degree relative	OR Adenocarcinoma 2,49 Adenosquamous 9,93 Squamous cell 3,11	 NS 0,05 0,05	 1 case in 40 2 cases in 23 13 cases in 418 9 controls in 801
13. Yoo KY et al. (1997)	First-degree relative	OR 2,20	1,21-4,01	18 cases in 203 44 controls in 827

Table 3. Risk of Cervical Cancer Among Relative Associated to Family History of Any Cancer (discordant cancer site)

Author (year)	relative with cancer	Effect	95% CI	number of events
1. Goldgar DE et al. (1994)	first-degree relative with			
	lung cancer	FRR 1,64	1,2-2,2	44
	colon cancer	FRR 1,49	1,1-1,9	51
2. Hemminki K., et al. (1997)	prostate cancer among fathers	mother with no cancer		
		RR* 1,0	0,7-1,2	68
		mother with any cancer		
		RR* 1,9	1,1 - 2,7	27
3. Hemminki K., et al. (1998a)		risk for *in situ* cervical cancer		
	father with oral cancer	FRR 1,2	1,1-1,3	458
	mother with oral cancer	FRR 1,4	1,2-1,6	139
	father with lung cancer	FRR 1,2	1,2-1,3	1355
	mother with lung cancer	FRR 1,4	1,3-1,5	534
4. Hemminki K., et al. (1999a)		risk for *in situ* cervical cancer		
	mother with lung cancer	FRR 1,38	1,27-1,50	593
	mother with urinary bladder cancer	FRR 1,17	1,02-1,32	243
	mother with oral cancer	FRR 1,38	1,16-1,61	153
		risk for invasive cervical cancer		
	mother with lung cancer	FRR 1,80	1,31-2,42	44
	mother with liver cancer	FRR 1,72	1,20-2,40	35
	mother with skin cancer	FRR 2,42	1,55-3,60	24
		risk for *in situ* cervical cancer		
	daughter with lymphoma	FRR 1,65	1,25-2,14	57
	daughter with ovary cancer	FRR1,38	1,02-1,82	50
	daughter with oral cancer	FRR 2,16	1,08-3,86	11
		risk for invasive cervical cancer		
	daughter with lung cancer	FRR 2,66	1,63-4,11	20
	daughter with skin cancer	FRR 2,8	1,21-5,51	8
	daughter with rectum cancer	FRR 2,4	1,03-4,72	8
	daughter with anus cancer	FRR 5,36	1,46-13,72	4

Author (year)	Relative with cancer	Effect	95% CI	number of events
5. Dong C. et al. (2001)	Parent with liver cancer	SIR 1,40	1,09-1,77	69
	Parent with lung cancer	SIR 1,28	1,08-1,51	143
6. Hemminki K., et al. (2001)		risk for *in situ* cervical cancer		
	Mother with lung cancer	SIR 1,29	1,19-1,38	724
	Mother with oral cancer	SIR 1,19	1,02-1,37	184
	Father with oral cancer	SIR 1,12	1,03-1,21	593
	Father with lung cancer	SIR 1,14	1,09-1,19	1785
		risk for invasive cervical cancer		
	Mother with liver cancer	SIR 1,46	1,03-1,95	38
	Mother with skin cancer	SIR 1,65	1,08-2,34	26
	Father with lung cancer	SIR 1,26	1,02-1,52	98

Abbreviations:
MRG - median of the distribution of the rate of the case GIF to the 100 controls GIFs
GIF - mesasure the degree of family clustering
CI - 95% confidence interval
FHR - familial hazard ratio
FRR - familial relative risk
RR - rate ratio
* RR - relative risk
R - tetrachoric correlation
SIR - standardized incidence ratios
SCC - squamous cell cancer
Adeno - Adenocarcinoma
OR - Odds ratio
MZ - monozygotic twins
DZ - dizygotic twins

Capítulo IV – ARTIGO II

Family History as a Co-factor for Adenocarcinoma and Squamous Cell Carcinoma of the Uterine Cervix: Results from Two Studies Conducted in The United States and Costa Rica.

Alice de M. Zelmanowicz, M.D.[1] and Allan Hildesheim, Ph.D.[2]

Affiliations of authors:

[1]Programa de Pós-graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul

[2] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Correspondece to:

Alice de M. Zelmanowicz, M.D., Programa de Pós-graduação em Epidemiologia Universidade Federal do Rio Grande do Sul

Keywords: cervical carcinoma, family history, attributable risk fraction

Running title: Family History and Cervical Cancer

ABSTRACT:

Cervical cancer has a known causal agent, Human Papillomavirus. Perhaps, genital infection by this virus is highly common. Just a few women will have persistent infection and much lesser will develop pre-malignant lesions and cancer. Several co-factor to cervical cancer have been studied and are well established. Family history of cancer is a common risk factor for other tumors and it is not completely related to cervical cancer. To evaluate the association between family history of cervical cancer and other gynecological cancer and risk of cervical neoplasia, data from two different studies were evaluated: a multicenter case-control study in Eastern United States and a cross-sectional study in Guanacaste, Costa Rica. Polytomous Regression was used to analyse the 3-levels outcomes and traditional Logistic Regression for dichotomous outcomes. Several confounding variables were tested but did not alter significantly the results. Overall, both studies showed a positive association with squamous cervical cancer after adjusted to HPV status and other variables. This is higher among sisters and pre-menopausal women. There is no association of cancer family history and adenocarcinoma of the cervix.

Introduction:

Cervical cancer is an important public health problem worldwide as it is the main cause of cancer death among women in many developing countries (Parkin D.M; Bray F.I. and Devesa S.S., 2001). Human Papillomavirus (HPV) is recognized as the leading cause of cervical cancer (Munoz N. et al. 2002; IARC, 1995). Knowledge that infection with one of about 15 oncogenic types of HPV is necessary for the development of cervical cancer has lead to the possibility of cervical cancer prevention through vaccination and/or screening for presence of the virus. However, from an etiological perspective, much remains to be learned about the pathogenesis of cervical cancer, and in particular about co-factors that, along with HPV infection lead to the development of this tumor.

HPV infection is a very common sexual transmitted infection that in the vast majority of instances resolves spontaneously. Only a small fraction of women infected with HPV have persistent infection that progress to pre-cancer and cancer. Understanding the co-factors that determine whether an HPV infection is likely to persist and progress would lead to a better understanding of cervical cancer etiology and could serve as a model for our understanding of tumors that are caused by viruses. Several co-factors have been evaluated to date including viral, host, and other exogenous factors. Well-established co-factors associated with the development of cervical cancer include HPV variants, smoking, high parity, and long-term oral contraceptive use (Castellsagué X and Munoz N, 2003). Infection with other sexually transmitted agents such as Herpes Simplex Virus type 2 (HSV-2) and *Chlamydia trachomatis* (Smith J.S. et al, 2002a and 2002b), and some nutritional factors might also be associated with risk of disease (Castle PE and Giuliano AR, 2003).

Familial aggregation of cervical cancer has been reported in the literature from record linkage studies in Scandinavia and the United States (Hemminki K. and Czene K., 2002 and Cannon-Albright LA. et al., 1994). These studies suggest that a family history of cervical cancer might increase risk of disease. Since familial aggregation could be a result of genetic predisposition among family members and/or shared environmental exposures and lifestyle factors, it is currently not known whether the

aggregation observed for cervical cancer is due to genetic or environmental effects. However, in support of an underlying genetic explanation for the observed familial aggregation, one study observed stronger effects when biological mothers/sisters were evaluated compared to non-biological and “half” relatives. Also, studies have reproducibly shown associations between human leukocyte antigen (HLA) alleles and risk of cervical cancer and pre-cancer, further supporting the role of inherited genetic factors in the etiology of this disease (Wang S.S and Hidesheim A., 2003; Magnusson P.K. et al. 1999).

Most studies of cervical cancer and pre-cancer that have evaluated the role of family history have focused on squamous cell tumors, since this histological form of cervical cancer comprises approximately 85-90% of all cervical tumors diagnosed each year. In contrast to squamous cell carcinomas of the cervix, the association between family history of cancer and risk of cervical adenocarcinomas and adenosquamous carcinomas (tumors with mixed squamous and glandular components) has been infrequently studied. Adenocarcinomas and adenosquamous carcinomas of uterine cervix have been shown to be linked to infection with HPV, but the co-factors associated with these glandular tumors have been shown to vary from those seen for squamous cell tumors (Lacey J.V. et al, 1999). It is unclear whether family history of cervical or other cancers is associated with risk of subsequent development of cervical adenocarcinomas and adenosquamous carcinomas, although limited evidence does exist in support of such an association (Brinton L et al., 1987).

The objective of the present study was to evaluate whether family history of cervical or other cancers is associated with cervical cancer of squamous or glandular origin. For this purposes, data from two large studies was evaluated: a multicenter case-control study of in situ and invasive squamous and adenocarcinomas conducted in the United States and a case-control study of squamous cervical cancers and their precursors nested within a population-based cohort of 10,000 women in Costa Rica.

Materials and Methods:

To evaluate the association between a family history of cervical and other cancers and risk of cervical neoplasia, data from two independently conducted studies were evaluated. The first study is a multicenter case-control study conducted in the Eastern United States to evaluate risk factors for *in situ* and invasive cervical cancer by histology (Lacey JV et al, 1999). The second is a population-based cohort study conducted in Guanacaste, Costa Rica to evaluate risk factors for HPV infection and progression of HPV infection to high-grade precancer and cervical cancer (Herrero, R., 2000). Each is discussed in turn below.

Eastern U.S. Study (Lacey JV et al, 1999): This study was designed with the primary intent of assessing the similarities and differences in risk factor profile between *in situ* and invasive adenocarcinomas (including adenosquamous carcinomas and other carcinomas with a glandular component) and squamous cell carcinomas. This study included women between the ages of 18 and 69 diagnosed with cervical cancer at one of six participating medical centers in the Eastern United States. All *in situ* or invasive incident, primary adenocarcinomas of uterine cervix and other carcinomas demonstrating glandular involvement and diagnosed between January 1, 1992 and March 1, 1996 were eligible. Women with endometrial cancer, sarcoma, fibroma, myoma or lymphoma were not eligible for study. Cases were retrospectively ascertained between January 1992 and June 1994 and prospectively ascertained between July 1994 and March 1996. To confirm the accuracy of the initial pathological diagnosis obtained from each participating clinical center, a panel of three expert pathologists jointly reviewed pathological specimens retrieved specifically for this purposes. At the time of review, a consensus diagnosis was obtained for each case reviewed and established the study diagnosis. 88% of cases were successfully reviewed; pathology specimens were unavailable for panel review for the remaining 12%. For these cases the initial local clinical center diagnosis was used as the final study diagnosis. For the 88% of cases reviewed by the expert panel, panel review invariably confirmed the initial diagnosis reported from the local participating clinical centers.

A second case group was comprised of women diagnosed with *in situ* or invasive squamous cell carcinoma (SCC) of the cervix. The same eligibility criteria

were applied to this second case group as were applied to the adenocarcinomas. Due to the excess of squamous cell carcinomas relative to adenocarcinomas, squamous cell carcinoma cases were matched to adenocarcinoma cases at a 1:1 ratio. Squamous cases were matched to adenocarcinomas on study center, age at diagnosis, date of diagnosis, and stage of disease at diagnosis (*in situ* versus invasive). For SCC cases, the initial pathological diagnosis reported by the participating clinical centers was used as the final study diagnosis. Review of a 10% subset of SCC cases by our expert panel confirmed the accuracy of the local clinical center diagnoses.

Control women consisted of healthy women identified through random-digit dialing and matched to adenocarcinoma cases at a 2:1 ratio. Controls were matched to adenocarcinoma cases on age, ethnicity and telephone exchange. Controls who reported a previous hysterectomy were not eligible for study.

The final analytic group included 124 adenocarcinomas, 33 adenocarcinoma *in situ* and 91 invasive tumors (response rate: 66%), 139 SCC, 48 carcinoma *in situ* and 91 invasive tumors (response rate: 54%) and 307 community controls (response rate: 76%).

All participants completed an in-person interview administered by trained study personnel where risk factor and socio-demographic information was assessed after an informed consent was signed. Information on family history of any cancer was collected. For women who reported having a family history of cancer, the type of cancer and type of relative was assessed. All reported exposures were truncated 12 months prior to the diagnosis date (for cases) or and equivalent date (for controls) to avoid collecting information on exposures that occurred after disease occurrence. Cervicovaginal cells were collected from cases and controls by clinician and/or self-administered sampling and used for HPV DNA testing by PGMY L1 primer PCR, as previously described (Gravitt PE et al, 1998).

Institutional Review Boards (IRBs) at the National Cancer Institute and each participating clinical center approved the study. All participants provided informed consent.

Costa Rican Cohort Study (Herrero R et al., 1997 and Herrero R. et al. , 2000):
A population-based cohort was established in Guanacaste, Costa Rica in 1993/4 to study the natural history of HPV and HPV-induced cervical neoplasia . The NCI and local IRBs reviewed and approved the study and all participants provided informed

consent. In this study, cluster sampling was utilized to select a representative sample of the adult female population of Guanacaste (N=10,738 eligible women). 10,049 women (94% of eligibles) agreed to visit one of the study clinics.

Participants responded to a risk factor questionnaire that assessed information on socio-demographic and risk factor information, like sexual behavior, smoking, parity and oral contraceptive use. Sexually active women underwent a pelvic examination, at which time a conventional Pap smear was prepared, cells were collected for semi-automated ThinPrep cytology (Cytyc Corp., Boxborough, MA), Cervigrams (National Testing Laboratories, Fenton, MO) were taken, and cervical cells were collected for HPV DNA Hybrid Capture Tube test (Cox et al, 1995) and HPV DNA testing by L1 consensus primer PCR (Herrero R. et al 2000). 291 women who refused to have a pelvic exam or for whom physical problems prevented a pelvic exam, and 621 women who reported having a hysterectomy were excluded from our study. Pelvic exam was also not performed on 583 self-reported virgins; these women were also excluded from the present study.

Women with cervical abnormalities at the time of the enrollment pelvic exam by visual inspection, cytology (conventional and/or ThinPrep) or cervicography, or who were in a 2% random sample of the population were referred to colposcopy, at which time a second more detailed questionnaire was administered which obtained additional information on cervical cancer risk factors, including family history of gynecologic cancers among first degree female relatives. For women who responded positively to the question on whether they had a family history of gynecologic cancer, further questions were asked to ascertain the type of cancer and relative affected. Since only women referred to colposcopy were administered the more detailed questionnaire that included questions on family history of cancer, the present study is restricted to the 2656 women who were refereed to colposcopy for evaluation during the enrollment phase of our cohort study.

Lesions visible at colposcopy were biopsied. Based on review of cytology, Cervigram and histology, each woman was assigned a diagnosis. Women with evidence of CIN2+ were treated as needed. A single pathologist at NCI reviewed diagnostic material to establish a final study diagnosis (Sherman ME et al., 1998). This final diagnosis was defined based on histology or cytology, when cytological results were confirmed by more than one method of evaluation. Thus, all cancers and 93% of all high-grade diagnoses were defined histologically. 39% of low-grade

lesions were defined by histology while the remainder of the low-grade lesions was defined by cytology that was confirmatory by more than one method of evaluation. For women diagnosed with high-grade disease, materials were re-reviewed by a second US pathologist, who distinguished CIN2 from CIN3 lesions.

In all, 12 women in our cohort were diagnosed with cervical cancer, 73 with CIN3, 56 with CIN2, and 189 with low-grade disease. The remaining participants in the present study had equivocal lesions or were found to be normal upon careful evaluation (n=1750)

For the analysis, we classified women into three groups. The first included the 12 women with screening detected invasive cancer and the 73 women with a final diagnosis of CIN3, the second included the 56 women with a final diagnosis of CIN2. The third included all remaining women initially referred to colposcopy but found upon further evaluation to have a final diagnosis of LSIL, equivocal lesions or normal (n=1939). This last group was considered the control group in analysis. Women with CIN2 were evaluated separately from women with CIN3 because of evidence suggesting that CIN2 is a highly misclassified diagnosis consisting of a mixture of true CIN1 and CIN3 lesions. Thus, to avoid misclassification in our definition of our case and control groups, we chose to evaluate CIN2 cases as a distinct category in analysis.

Statistical analysis:

Polytomous Logistic Regression models (also called Multinomial Logistic Regression) (Hosmer, D.W. and Lemeshow, S, 2000) were used to estimate odds ratios (ORs) and 95% conficence intervals (95% CI) when evaluating the association between a family history of cancer and risk of disease. Polytomous logistic regression was chosen over standard or conditional logistic regression because the outcome variables for both studies involved nominal response variables with more than two categories (adenocarcinoma, SCC, and controls for the Eastern US study; CIN3/cancer, CIN2, and controls for the Costa Rican study). This approach is a preferred alternative to a two-outcome logistic model where dichotomization is arbitrary. Standard logistic regression was used when polytomous models could not be generated due to zero cells in one of the disease categories.

The following cervical cancer risk factors were evaluated as potential confounders of the family history-disease association: age (50 year-old or less versus older than 50 years), number of partners (1 versus 2 or more partners), smoking (ever versus never smoke), oral contraceptive use (ever versus never use OC), number of pregnancies (up to 2 versus 3 or more), Papanicolau exams in the past (less than 2 versus 2 or more. To evaluate the possibility of confounding by these factors, models were generated that included the family history variable of interest and each of the potential confounders. When examined in this manner, none of the potential confounders evaluated altered the OR estimate associated with family history by more than 15% (tables 7 and 8). Unadjusted estimates of risk are therefore presented in the results that follow. Given the modest size of our two studies and the fact that family history of cancer is a low prevalence event, it was not possible for us to evaluate the possibility of confounding further, by creating models that adjusted for multiple potential confounding factors simultaneously.

The potential for effect modification by important factors was evaluated by stratification. Factors that were evaluated for potential effect modification include menopausal status and stage of disease. In addition, since HPV is a necessary cause of invasive cervical cancer and its precursor lesions (i.e. 100% of cases are positive for HPV), the effect of HPV infection on the family history effect was evaluated by stratification rather than statistical adjustment (i.e., in analysis restricted to all cases and HPV positive controls).

SAS (version V8.2) system computed all analyses.

Results:

Eastern U.S. Study:

Detailed demographic characteristics were previously reported (Lacey J.V., 1999). In brief, ethnicity, education and income varied slightly between cases groups and community controls. Adenocarcinoma case group and controls were more educated and had a higher income than SCC case group. African American ethnicity was more common among SCC cases than controls and Adenocarcinoma cases (6,5% of Adenocarcinoma cases, 9,2% of controls and 13,0 of SCC cases).

As summarized in Table 1, a family history of cervical cancer was positively associated with SCC (OR 2,6, 95% CI 1,1-6,2) but not with adenocarcinoma (OR =

1,4; 95% CI = 0,48-3,8). The observed association was of similar magnitude, regardless of whether history of cervical cancer was reported among a mother, sister, or daughter. No significant association was observed between a family history of gynecological tumors other than cervical cancer and either SCC or adenocarcinoma (OR = 1,2 for SCC; 95% CI = 0,39-3,5 and OR = 1,6 for adenocarcinoma; 95% CI = 0,59-4,2)

Stratified analyses were performed to evaluate whether the effect between family history and SCC was observed in analysis restricted to HPV positive women (table 2), and whether similar effects were observed in premenopausal and postmenopausal women (table 3). Additional stratified analysis examined whether effects were seen for both in situ and invasive tumors (table 2). These stratified analyses evaluated risk associated with a family history of any gynecological tumor, since small numbers precluded stratified analyses that evaluated family history of cervical cancer alone. In HPV-restricted analyses, elevations in risk remained, but were attenuated and no longer reached statistical significance (OR = 1,5, 95% CI = 0,47-4,7 in analysis restricted to control women positive for any HPV and OR = 1,4, 95% CI = 0,37-5,0 in analysis restricted to control women positive for oncogenic HPV). Effects were strongest among premenopausal women (OR = 2,5; 95% CI = 1,1-5,5) and in analysis restricted to invasive SCC (OR = 2,3; 95% CI = 1,1-4,7). Analysis stratified by age ($\geq$50 years and <50 years) produced results similar to those observed for menopausal status (i.e. effect stronger among younger women; data not shown).

Costa Rican Cohort Study

The median age of the women was 37 years. Women in our study were highly parous (median number of pregnancies = 4). Most women reported having used oral contraceptives (63%) and less then 11% had ever smoked. More than half of the participants reported only one lifetime sexual partner and 87% reported having had a Papanicolau test prior to enrollment in our study (Herrero R et al. 2000).

In an interview conducted at the time of colposcopic evaluation and before diagnosis was known, women were asked about their family history of gynecological cancers. Results are summarized in tables 3-6.

A family history of cervical or other gynecological tumors was positively associated with CIN3/cancer, but not with CIN2 (table 4). Women who reported a family history of cervical cancer had an OR of 3,2 (95% CI = 1,1-9,2) for CIN3/cancer. Those who reported a history of gynecological cancers other than cervical cancer had an OR of 2,0 (95% CI = 0,86-4,8) for CIN3/cancer. Elevations in risk were observed regardless of whether history of gynecological cancers was reported among a mother, sister, or daughter.

Stratified analyses were performed to evaluate whether the effect between family history of gynecological tumors and CIN3/cancer was observed in analysis restricted to HPV positive women (table 5), and whether similar effects were observed in premenopausal and postmenopausal women (table 6). These stratified analyses evaluated risk associated with a family history of any gynecological tumor, since in our Costa Rican study a history of either cervical or other gynecological tumors was observed to be positively associated with risk. In HPV-restricted analyses, elevations in risk remained, regardless of whether controls were restricted based on the presence of any HPV (OR = 2,4; 95% CI = 1,1-4,9) or of oncogenic types of HPV (OR = 2,5; 95% CI = 1,1-5,3). Elevations in risk associated with a family history of gynecological tumors were also observed for both premenopausal and postmenopausal women, although the magnitude of the effect appeared strongest and was only statistically significant in analysis restricted to postmenopausal women (table 6). Similar patterns were observed when analyses stratified by age were performed ($\geq$50 years and <50 years; data not shown).

Discussion:

Few epidemiological studies investigated the association between family history of cancer and risk for cervical cancer as its main objective. Those that have done do not have HPV status information (Brinton L. A. et al., 1987 and Yoo KY et al., 1997) to include in the analysis. Studies of Cancer Register Database from USA and Scandinavian countries reported a two-fold risk for cervical cancer for women who has family history of same cancer (Hemminki K. and Czene K., 2002, Magnusson, P.K. et al., 2000 e Magnusson,P.K., Sparen,P. and Gyllensten,U.B.,1999) mainly for *in situ* and squamous cell carcinoma. Twins

studies in the same Scandinavian databases reported contradictory results for this association (Lichtenstein P. et al., 2000 and Ahlborn et al., 1997).

The present analyses used two epidemiological studies. The Costa Rican Study performed multiple screening techniques and carried out extensive diagnostic work-ups to ensure completeness of case identification and classification. In this study they also performed HPV testing for all women with abnormal cervical diagnoses and a 2% random sample of the entire cohort as controls (Herrero R, 2000). And the multicenter case-control study conducted in the Eastern United States where all histological slides were reviewed by a pathologist panel to reduce misclassification of the rare adenocarcinoma subtype and collected material for HPV test the majority of subjects was done (Lacey J.V., 2001).

The results reveal a positive association between family history of cervical cancer and risk of cervical squamous cell carcinoma in both studies. Numbers were too small to firmly confirm that this association is stronger when the family history occurs among mothers or sisters even when exposition is gynecological cancer as a group.

When the analysis is restricted to HPV positive controls, this association is not statistically significant any more for SCC or Adenocarcinoma tumors but it is elevated in the Costa Rican study even for HPV oncogenic types. This discrepancy could be explained by the small numbers among HPV positive controls in the US study or because of different population characteristics.

To study the effect of age and/or exogenous hormone on this association, stratified analysis by menopausal status was performed. Discordant results can be seen in the two studies. A risk relative of 4,1 is associated with cancer in the Costa Rican Study for pos-menopausal women and an OR of 2,1 for pre-menopausal women in the American study. Heterogeneity test was carryout and results reveal that these two odds ratio are not statically different. Nevertheless, differences between results of these two databases when it is analyzed by menopausal status can represent differences in the population. Sexual practices are probably different in these two countries and age at HPV exposition and differences in co-factors as tobacco use could modify the natural history of this disease. But probably it is just effect of lack of power (small numbers on each category).

This analysis has several strengths. It is the first study which all the participants have their HPV status and screening practices assessed. Besides, most

of the subjects had the cancer family history ascertained before the diagnostic, pathological diagnostic were full revised, one study was population-based and other involved several different hospitals with population controls.

Virus infection, as HPV, can aggregate in families for several reasons. It can spread in some non-sexual ways, sexual practices can be culturally defined and also immune response to infection has probably hereditary influence. Therefore, association of family history of cervical cancer and risk of cervical cancer could be a residual effect of HPV infection. Association of family history of other cancers related to HPV infection as anal and oral cancer and risk for cervical cancer has been described (Hemminki K., et al. 1999).

Cancer family history is rare and both studies have few numbers for this variable. Inconsistency could be attributed just because of the small numbers. Recall bias is particularly possible in the Eastern U.S. Study database as most of the women were interviewed after they had already known their cancer diagnostics.

In summary, this study reported similar results with the previous published studies. Probably, the Costa Rican cohort will be possible to confirm these results after its follow-up phase is finished. As family history of cervical cancer as was assessed in this analysis is confirmed as risk factor for cervical cancer we will have more consistency information for the genetic influence on this disease.

References:

1. Bosch, F. X. and de Sanjose, S. Chapter 1: Human papillomavirus and cervical cancer--burden and assessment of causality. J.Natl.Cancer Inst.Monogr 2003;3-13.
2. Brinton, L. A., Tashima, K. T., Lehman, H. F., Levine, R. S., Mallin, K., Savitz, D. A., Stolley, P. D., and Fraumeni, J. F., Jr. Epidemiology of cervical cancer by cell type. Cancer Res. 1987; 47:1706-1711.
3. Castellsagué, X. and Muñoz, N. Cofactor in Human Papillomavirus Carcinogenesis – Role of Parity, Oral Contraception and Tobacco Smoking. J.Natl.Cancer Inst.Monogr 2003; 20-28

4. Castle, P.E. and Giuliano, A.R. Genital Tract Infections, Cervical Inflammation, and Antioxidant Nutrients – Assesing Their Roles as human papillomavirus Cofactors. J.Natl.Cancer Inst.Monogr 2003;29-34
5. Cannon-Albright, L.A., Thoams, A., Goldgar, D.E., et al. Familiality of Cancer in Uthah. Cancer Res 1994; 54:2378-85
6. Cox, J. T., Lorincz, A. T., Schiffman, M. H., Sherman, M. E., Cullen, A., and Kurman, R. J. Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance. Am.J.Obstet.Gynecol. 1995; 172:946-954.
7. Gravitt, P. E., Peyton, C. L., Apple, R. J., and Wheeler, C. M. Genotyping of 27 human papillomavirus types by using L1 consensus PCR products by a single-hybridization, reverse line blot detection method. J.Clin.Microbiol. 1998; 36:3020-3027.
8. Hemminki, K., Dong, C., and Vaittinen, P.Familial risks in cervical cancer: is there a hereditary component? Int.J.Cancer 1999; 82:775-781.
9. Hemminki, K. and Czene, K. Attributable risks of familial cancer from the Family-Cancer Database. Cancer Epidemiol.Biomarkers Prev. 2002; 11:1638-1644.
10. Herrero, R., Hildesheim, A., Bratti, C., Sherman, M. E., Hutchinson, M., Morales, J., Balmaceda, I., Greenberg, M. D., Alfaro, M., Burk, R. D., Wacholder, S., Plummer, M., and Schiffman, M. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. J.Natl.Cancer Inst. 2000; 92:464-474.
11. Herrero, R., Schiffman, M. H., Bratti, C., Hildesheim, A., Balmaceda, I., Sherman, M. E., Greenberg, M., Cardenas, F., Gomez, V., Helgesen, K., Morales, J., Hutchinson, M., Mango, L., Alfaro, M., Potischman, N. W., Wacholder, S., Swanson, C., and Brinton, L. A.Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: the Guanacaste Project. Rev.Panam.Salud Publica 1997; 1:362-375.
12. Hosmer, D.W., and Lemeshow, S. Applied logistic regression. Second Edition. 2000. New York: Wiley.
13. International Agency for Rsearch on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans. Human papillomaviruses. IARC monographs on the evaluation of carcinogenic risks to humans. Vol.64.Lyon (France): IARC; 1995

14. Lacey, J. V., Jr., Brinton, L. A., Abbas, F. M., Barnes, W. A., Gravitt, P. E., Greenberg, M. D., Greene, S. M., Hadjimichael, O. C., McGowan, L., Mortel, R., Schwartz, P. E., Silverberg, S. G., and Hildesheim, A.Oral contraceptives as risk factors for cervical adenocarcinomas and squamous cell carcinomas. Cancer Epidemiol.Biomarkers Prev. 1999; 8:1079-1085.
15. Magnusson, P. K., Sparen, P., and Gyllensten, U. B.Genetic link to cervical tumours. Nature 1999; 400:29-30.
16. Munoz, N., Franceschi, S., Bosetti, C., Moreno, V., Herrero, R., Smith, J. S., Shah, K. V., Meijer, C. J., and Bosch, F. X. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet 2002; 359:1093-1101.
17. Parkin, D. M., Bray, F. I., and Devesa, S. S. Cancer burden in the year 2000. The global picture. Eur.J.Cancer 2001; 37 Suppl 8:S4-66.
18. Shreman, M.E., Schiffman, M., Herrero, R., Kelly, D., Bratti, C, Mango,L.J., Alfaro, M., Hutchinson, M.L., Mena, F., Hildesheim, A., Morales, J., Greenberg, M.D., Balmaceda, I. And Lorincz, A.T. Performance of a Semiautomated Papanicolau Smear Screening System. Cancer (Cancer Cytopathology). 1998; 84 (5):273-280.
19. Smith, J. S., Herrero, R., Bosetti, C., Munoz, N., Bosch, F. X., Eluf-Neto, J., Castellsague, X., Meijer, C. J., Van den Brule, A. J., Franceschi, S., and Ashley, R. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. J.Natl.Cancer Inst. 2002a; 94:1604-1613.
20. Smith, J. S., Munoz, N., Herrero, R., Eluf-Neto, J., Ngelangel, C., Franceschi, S., Bosch, F. X., Walboomers, J. M., and Peeling, R. W.Evidence for Chlamydia trachomatis as a human papillomavirus cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. J.Infect.Dis. 2002b; 185:324-331.
21. Wang, S. S. and Hildesheim, A.Chapter 5: Viral and host factors in human papillomavirus persistence and progression. J.Natl.Cancer Inst.Monogr 2003;35-40.

Table 1. Association Between Family History of Cancer and Histological Subtypes of Carcinoma of the Cervix
Results from the Multicentric Study in the Eastern United States

	Controls	Adenocarcinoma			Squamous		
	N	N	OR	95% CI	N	OR	95% CI
No Family History of Gynecological Cancer	285	127	1,0		121		
Family History of Other Gynecological Tumors	10	7	1,6	0,59-4,2	5	1,2	0,39-3,5
Family History of Cervical Cancer	10	6	1,4	0,48-3,8	11	2,6	1,1-6,3
No Family History of Gynecological Cancer	285	127	1,0		121		
Family History of Gynecological Cancer							
among Mother	13	12	2,1	0,92-4,7	9	1,6	0,68-3,9
among Sister	6	2	0,75	0,15-3,8	6	2,4	0,75-7,5
among Daughter	1	0			1	2,4	0,14-38,0

Table 2. Association Between Family History of Cancer and Histological Subtypes of Carcinoma of the Cervix Among Selected Subgroups of Women. Results from the Multicentric Study in the Eastern United States							
	Controls	Adenocarcinoma			Squamous		
	N	N	OR	95% CI	N	OR	95% CI
Restricted to Invasive Cancers							
No Family History of Gynecological Cancer	285	94	1,1		78	1,0	
Family History of Gynecological Cancer	21	11	1,6	0,74-3,4	13	2,3	1,1-4,7
Restricted to In Situ Cancers							
No Family History of Gynecological Cancer	285	35	1,0		44	1,0	
Family History of Gynecological Cancer	21	2	0,78	0,17-3,5	3	0,93	0,27-3,2
Restricted to HPV(+) Controls							
No Family History of Gynecological Cancer	45	129	1,0		122	1,0	
Family History of Gynecological Cancer	4	13	1,1	0,35-3,7	16	1,5	0,47-4,7
Restricted to Oncogenic HPV(+) Controls							
No Family History of Gynecological Cancer	31	129	1,0		122	1,0	
Family History of Gynecological Cancer	3	13	1,0	0,28-3,9	16	1,4	0,37-5,0

Table 3. Association Between Family History of Cancer and Histological Subtypes of Carcinoma of the Cervix Among Women stratified for Menopausal Status. Results from the Multicentric Study in the Eastern United States

	Control N	Adenocarcinoma N	OR	95% CI	Squamous N	OR	95% CI
Restricted to Premenopausal Women							
No Family History of Gynecological Cancer	248	108	1,0		101	1,0	
Family History of Gynecological Cancer	13	9	1,6	0,66-3,8	13	2,5	1,1-5,5
Restricted to Postmenopausal Women							
No Family History of Gynecological Cancer	35	21	1,0		19	1,0	
Family History of Gynecological Cancer	7	4	0,95	0,25-3,7	3	0,79	0,18-3,4

Table 4. Association Between Family History of Cancer and Varying Grades of Cervical Neoplasia
Results from the Population-Based Study in Costa Rica

	Controls	CIN 2			CIN3/Cancer		
	N	N	OR	95% CI	N	OR	95% CI
No Family History of Gynecological Cancer	1836	53	1,0		75	1,0	
Family History of Other Gynecological Tumors	72	3	1,4	0,44-4,7	6	2,0	0,86-4,8
Family History of Cervical Cancer	31	0	0	0	4	3,2	1,1-9,2
No Family History of Gynecological Cancer	1836	53	1,0		75	1,0	
Family History of Gynecological Cancer							
among Mother	76	2	0,91	0,22-3,8	6	1,9	0,82-4,6
among Sister	29	1	1,2	0,16-8,9	3	2,5	0,75-8,5
among Daughter	2	0	0	0	1	12,2	1,1-136,5

Table 5. Association Between Family History of Cancer and Varying Grades of Cervical Neoplasia Among Selected Subgroups of Women. Results from the Population-Based Study in Costa Rica							
	Controls	CIN 2			CIN 3/Cancer		
	N	N	OR	95% CI	N	OR	95% CI
Restricted to HPV(+) Controls							
No Family History of Gynecological Cancer	691	53	1,0		75	1,0	
Family History of Gynecological Cancer	39	3	0,89	0,27-2,9	10	2,4	1,1-4,9
Restricted to Oncogenic HPV(+) Controls							
No Family History of Gynecological Cancer	406	53	1,0		75	1,0	
Family History of Gynecological Cancer	22	3	0,85	0,25-2,9	10	2,5	1,1-5,3

Table 6. Association Between Family History of Cancer and Varying Grades of Cervical Neoplasia Among Women Stratified for Menopausal Status. Results from the Population-Based Study in Costa Rica

	Controls	CIN 2			CIN 3/Cancer		
	N	N	OR	95% CI	N	OR	95% CI
Restricted to Premenopausal Women							
No Family History of Gynecological Cancer	1529	39	1,0		58	1,0	
Family History of Gynecological Cancer	85	3	1,3	0,41-4,4	6	1,8	0,77-4,4
Restricted to Postmenopausal Women							
No Family History of Gynecological Cancer	302	14			17	1,0	
Family History of Gynecological Cancer	18	0	0		4	4,1	1,3-13,6

Table 7. Analysis for Confounders. Results from the Multicentric Study in the Eastern United States										
Diagnostic	Family History of Cervical Cancer									
	Crude OR	Age	Race	Education	BMI	Previous Papanicolau	Smoke (ever X never)	Number of partners	OC (ever X never)	Number of pregnancies
Adeno	1,4	1,4	1,3	1,3	1,2	1,4	1,3	1,3	1,2	1,4
Squamous	2,6	2,6	2,5	2,3	2,5	2,6	2,6	2,6	2,6	2,5

Table 8 Analysis for Confounders. Results from the Population-Based Study in Costa Rica								
Diagnostic	Family History of Cervical Cancer							
	Crude OR	Age	Education	Previous Papanicolau	Smoke (ever X never)	Number of partner	OC (ever X never)	Number of pregnancies
CIN 2	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
CIN3/CA	3,2	3,2	3,2	3,2	3,3	3,3	3,3	3,3

Capítulo V - CONCLUSÕES

Concluindo, esta revisão da literatura e os estudos originais demonstram que história familiar de câncer de cérvice associa-se positivamente ao risco aumentado para desenvolver câncer de cérvice. Os estudos aqui analisados demonstram que esta associação é consistente, independente do método que ela é avaliada.

Esta elevação de risco está associada tanto à câncer invasivo quanto à *in situ,* o que afasta a possibilidade que este achado esteja relacionado exclusivamente a práticas de rastreamento mais intensas em famílias com história de câncer.

A associação entre história familiar de câncer de cérvice e risco para câncer de cérvice é positiva independente do tipo de relacionamento de primeiro grau: mães, irmãs ou filhas.

Resultados de estudos que avaliaram o grau de compartilhamento de características genéticas indicam que esta associação é, pelo menos em parte, devido a fatores genéticos. Se estes fatores genéticos determinam diretamente a resposta à infecção ou ao processo de malignização, ou influenciam outros fatores associados à persistência e progressão de lesões cervicais, não é possível pela presente tese ser definido.

O tipo de câncer mais fortemente associado a esta elevação de risco é o próprio câncer de cérvice porém outros cânceres ginecológicos também estão associados. O adenocarcinoma de cérvice uterina também está associado ao aumento de risco para câncer epidermóide, porém esta associação não é consistentemente reproduzida, talvez pelo pequeno número destes tumores. Este trabalho não permite avaliar se este sub-tipo histológico está associado ao aumento de risco do próprio adenocarcinoma de cérvice.

Porque esta exposição (história familiar) é rara, os estudos de base populacional são os que mais fortemente indicam que esta associação é estatisticamente significativa, porém o controle para fatores importantes como infecção pelo HPV e práticas de rastreamento é importante para diminuir a possibilidade de achados enviesados.

Capítulo VI – Considerações Finais

Esta tese teve por objetivo avaliar a associação entre história familiar de câncer e risco para câncer de cérvice uterina. Esta hipótese já tinha sido testada esporadicamente em estudos de registros de câncer e em alguns estudos observacionais sem o devido controle para os principais fatores de risco. Além disso, os resultados disponíveis eram inconsistentes e de difícil comparação.

No presente estudo, foi possível pela primeira vez sistematizar os resultados disponíveis na literatura, comparando resultados por estágio, parentesco e concordância. É possível que o método de sistematização não tenha captado a totalidade dos artigos que avaliaram esta associação por ter se limitado a busca ao MEDLINE. Além disso, devido às formas tão diversas de medir o efeito, não foi possível fazer uma meta-análise.

Foi possível também estudar de forma original esta associação em dois bancos de dados em que informações sobre infecção pelo HPV e outros co-fatores estavam disponíveis. Esta exposição é relativamente rara e por isso os números analisados eram pequenos, gerando intervalos de confiança amplos e por vezes não-significativos. Além disso, história familiar para a maioria das exposições avaliada através de entrevista pode ser influenciada por viés recordatório (*recall bias*), um tipo especial de viés de informação.

Foi encontrada uma associação entre história familiar de câncer de cérvice e câncer de cérvice, na mesma direção e magnitude semelhante em todos os estudos. Com isso, é possível considerar história familiar de câncer de cérvice um co-fator de câncer de cérvice de pequena a moderada grandeza.

Esta exposição, no entanto, é rara e pode-se atribuir menos de 1% a sua influência no conjunto de fatores que definem o processo de malignização, o que define que ela não possa definir um grupo de alto risco em que esforços preventivos devam ser intensificados.

Por outro lado, definir que história familiar é fator de risco para câncer de cérvice e que parte desta exposição é explicada pela susceptibilidade genética reforça a necessidade de se continuar os estudos que tentam definir os genes candidatos a estarem envolvidos neste processo.

Capítulo V - REFERÊNCIAS BIBLIOGRÁFICAS

1. Ahlbom, A., Lichtenstein, P., Malmstrom, H., Feychting, M., Hemminki, K., and Pedersen, N. L.Cancer in twins: genetic and nongenetic familial risk factors. J.Natl.Cancer Inst. 1997; 89:287-293.
2. Alvarez, R. D., Conner, M. G., Weiss, H., Klug, P. M., Niwas, S., Manne, U., Bacus, J., Kagan, V., Sexton, K. C., Grubbs, C. J., Eltoum, I. E., and Grizzle, W. E.The efficacy of 9-cis-retinoic acid (aliretinoin) as a chemopreventive agent for cervical dysplasia: results of a randomized double-blind clinical trial. Cancer Epidemiol.Biomarkers Prev. 2003; 12:114-119.
3. Auborn, K. J., Woodworth, C., DiPaolo, J. A., and Bradlow, H. L.The interaction between HPV infection and estrogen metabolism in cervical carcinogenesis. Int.J.Cancer 1991; 49:867-869.
4. Bosch, F. X. and de Sanjose, S. Chapter 1: Human papillomavirus and cervical cancer--burden and assessment of causality. J.Natl.Cancer Inst.Monogr 2003;3-13.
5. Bosch, F. X., Manos, M. M., Munoz, N., Sherman, M., Jansen, A. M., Peto, J., Schiffman, M. H., Moreno, V., Kurman, R., and Shah, K. V.Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J.Natl.Cancer Inst. 1995; 87:796-802.
6. Brasil. Ministério da Saúde. Instituto Nacional de Câncer- INCA, Estimativas de incidência e mortalidade por câncer. Rio de Janeiro: INCA, 2003.
7. Brinton, L. A.Epidemiology of cervical cancer--overview. IARC Sci.Publ. 1992;3-23.
8. Cambruzzi E. Adenocarcinoma Endocervical no Sul do Brasil: morfologia e prevalência. Porto Alegre, 2003. Dissertação (Mestrado) Fundação Faculdade Federal de Ciências Médicas de Porto Alegre. Programa de Pós-Graduação em Patologia: Anatomia Patológica e Citopatologia
9. Cannistra, S. A. and Niloff, J. M.Cancer of the uterine cervix. N.Engl.J.Med. 1996; 334:1030-1038.
10. Castellsague, X. and Munoz, N. Chapter 3: Cofactors in human papillomavirus carcinogenesis--role of parity, oral contraceptives, and tobacco smoking. J.Natl.Cancer Inst.Monogr 2003;20-28.

11. Castle, P. E. and Giuliano, A. R. Chapter 4: Genital tract infections, cervical inflammation, and antioxidant nutrients--assessing their roles as human papillomavirus cofactors. J.Natl.Cancer Inst.Monogr 2003;29-34.
12. Castle, P. E., Wacholder, S., Lorincz, A. T., Scott, D. R., Sherman, M. E., Glass, A. G., Rush, B. B., Schussler, J. E., and Schiffman, M.A prospective study of high-grade cervical neoplasia risk among human papillomavirus-infected women. J.Natl.Cancer Inst. 2002; 94:1406-1414.
13. Chan, P.G., Sung, H.Y., Sawaya, G.F. Changes in cervical cancer incidence after three decades of screening US women less than 30 years old. Obstet Gynecol. 2003; 102(4):765-73.
14. Daling, J. R. and Sherman, K. J. Relationship between human papillomavirus infection and tumours of anogenital sites other than the cervix. IARC Sci.Publ. 1992;223-241.
15. Drain, P. K., Holmes, K. K., Hughes, J. P., and Koutsky, L. A. Determinants of cervical cancer rates in developing countries. Int.J.Cancer 2002; 100:199-205.
16. Eichholzer, M., Luthy, J., Moser, U., and Fowler, B.Folate and the risk of colorectal, breast and cervix cancer: the epidemiological evidence. Swiss.Med.Wkly. 2001; 131:539-549.
17. Fletcher RH, Fletcher SW e Wagner EH. Epidemiologia Clínica:Elementos essenciais. Cap 8, p.174. 1996. Artes Médicas, Porto Alegre
18. Gustafsson, L., Ponten, J., Zack, M., and Adami, H. O.International incidence rates of invasive cervical cancer after introduction of cytological screening. Cancer Causes Control 1997; 8:755-763.
19. Hellberg, D., Nilsson, S., Haley, N. J., Hoffman, D., and Wynder, E. Smoking and cervical intraepithelial neoplasia: nicotine and cotinine in serum and cervical mucus in smokers and nonsmokers. Am.J.Obstet.Gynecol. 1988; 158:910-913.
20. Hemminki, K. and Czene, K.Attributable risks of familial cancer from the Family-Cancer Database. Cancer Epidemiol.Biomarkers Prev. 2002; 11:1638-1644.
21. Hemminki, K., Li, X., and Mutanen, P.Familial risks in invasive and in situ cervical cancer by histological type. Eur.J.Cancer Prev. 2001; 10:83-89.

22. Hildesheim, A., Hadjimichael, O., Schwartz, P. E., Wheeler, C. M., Barnes, W., Lowell, D. M., Willett, J., and Schiffman, M.Risk factors for rapid-onset cervical cancer. Am.J.Obstet.Gynecol. 1999; 180:571-577.
23. Hildesheim, A. and Wang, S. S. Host and viral genetics and risk of cervical cancer: a review. Virus Res. 2002; 89:229-240.
24. Hosmer, D.W., and Lemeshow, S. Applied logistic regression. Second Edition. 2000. New York: Wiley.
25. International Agency for Research on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans. Human papillomaviruses. IARC monographs on the evaluation of carcinogenic risks to humans. Vol.64.Lyon (France): IARC; 1995
26. Jemal, A., Murray, T., Samuels, A., Ghafoor, A., Ward, E., and Thun, M. J.Cancer statistics, 2003. CA Cancer J.Clin. 2003; 53:5-26.
27. Kalakun L. Mortalidade por Câncer de cérvice uterina no Rio grande do Sul, no período de 1979 a 1998. Porto Alegre, 2002. Dissertação (Mestrado) Universidade Federal do Rio Grande do Sul. Programa de Pós-Graduação em Medicina:Epidemiologia.
28. Lacey, J. V., Jr., Brinton, L. A., Abbas, F. M., Barnes, W. A., Gravitt, P. E., Greenberg, M. D., Greene, S. M., Hadjimichael, O. C., McGowan, L., Mortel, R., Schwartz, P. E., Silverberg, S. G., and Hildesheim, A.Oral contraceptives as risk factors for cervical adenocarcinomas and squamous cell carcinomas. Cancer Epidemiol.Biomarkers Prev. 1999; 8:1079-1085.
29. Lacey, J. V., Jr., Brinton, L. A., Barnes, W. A., Gravitt, P. E., Greenberg, M. D., Hadjimichael, O. C., McGowan, L., Mortel, R., Schwartz, P. E., Kurman, R. J., and Hildesheim, A. Use of hormone replacement therapy and adenocarcinomas and squamous cell carcinomas of the uterine cervix. Gynecol.Oncol. 2000; 77:149-154.
30. Lacey, J. V., Jr., Frisch, M., Brinton, L. A., Abbas, F. M., Barnes, W. A., Gravitt, P. E., Greenberg, M. D., Greene, S. M., Hadjimichael, O. C., McGowan, L., Mortel, R., Schwartz, P. E., Zaino, R. J., and Hildesheim, A. Associations between smoking and adenocarcinomas and squamous cell carcinomas of the uterine cervix (United States). Cancer Causes Control 2001; 12:153-161.

31. Lichtenstein, P., Holm, N. V., Verkasalo, P. K., Iliadou, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A., and Hemminki, K.Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N.Engl.J.Med. 13-7-2000; 343:78-85.
32. Magnusson, P. K., Lichtenstein, P., and Gyllensten, U. B.Heritability of cervical tumours. Int.J.Cancer 2000; 88:698-701.
33. Magnusson, P. K., Sparen, P., and Gyllensten, U. B.Genetic link to cervical tumours. Nature 1999; 400:29-30.
34. Munoz, N., Franceschi, S., Bosetti, C., Moreno, V., Herrero, R., Smith, J. S., Shah, K. V., Meijer, C. J., and Bosch, F. X. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet 2002; 359:1093-1101.
35. Palefsky, J. M. and Holly, E. A.Chapter 6: Immunosuppression and co-infection with HIV. J.Natl.Cancer Inst.Monogr 2003;41-46.
36. Parkin, D. M., Bray, F. I., and Devesa, S. S.Cancer burden in the year 2000. The global picture. Eur.J.Cancer 2001; 37 Suppl 8:S4-66.
37. Schlecht, N. F., Platt, R. W., Duarte-Franco, E., Costa, M. C., Sobrinho, J. P., Prado, J. C., Ferenczy, A., Rohan, T. E., Villa, L. L., and Franco, E. L.Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. J.Natl.Cancer Inst. 2003; 95:1336-1343.
38. Sherman, M. E., Lorincz, A. T., Scott, D. R., Wacholder, S., Castle, P. E., Glass, A. G., Mielzynska-Lohnas, I., Rush, B. B., and Schiffman M. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J.Natl.Cancer Inst. 2003; 95:46-52.
39. Shiffman, M. Epidemiology. In: Kurman R.J. Blaustein's pathology of the female genital tract. Fifth Edition. New York. Springer-Verlag New York, Inc. 2001. p.1301-1318
40. Smith, J. S., Green, J., Berrington, de Gonzalez, Appleby, P., Peto, J., Plummer, M., Franceschi, S., and Beral, V.Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet 2003; 361:1159-1167.
41. Smith, J. S., Herrero, R., Bosetti, C., Munoz, N., Bosch, F. X., Eluf-Neto, J., Castellsague, X., Meijer, C. J., Van den Brule, A. J., Franceschi, S., and Ashley, R.Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. J.Natl.Cancer Inst. 2002a; 94:1604-1613.

42. Smith, J. S., Munoz, N., Herrero, R., Eluf-Neto, J., Ngelangel, C., Franceschi, S., Bosch, F. X., Walboomers, J. M., and Peeling, R. W.Evidence for Chlamydia trachomatis as a human papillomavirus cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. J.Infect.Dis. 2002b; 185:324-331.
43. Solomon, D., Davey, D., Kurman, R., Moriarty, A., O'Connor, D., Prey, M., Raab, S., Sherman, M., Wilbur, D., Wright, T., Jr., and Young, N.The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002; 287:2114-2119.
44. Verkasalo, P. K., Kaprio, J., Koskenvuo, M., and Pukkala, E.Genetic predisposition, environment and cancer incidence: a nationwide twin study in Finland, 1976-1995. Int.J.Cancer 1999; 83:743-749.
45. Walboomers, J. M., Jacobs, M. V., Manos, M. M., Bosch, F. X., Kummer, J. A., Shah, K. V., Snijders, P. J., Peto, J., Meijer, C. J., and Munoz, N.Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J.Pathol. 1999; 189:12-19.
46. Wang S.W. and Hidesheim A. Viral and Host Factors in Human Papillomavirus Persistence and Progression. J.Natl.Cancer Inst.Monogr 2003; 31:35-40.
47. Wright, T.C., Ferenczy, A. and Kurman, R.J. Carcinoma and Other Tumors of the Cervix. In: Kurman R.J. Blaustein's pathology of the female genital tract. Fifth Edition. New York. Springer-Verlag New York, Inc. 2001. p325-381
48. Wright, T.C., Kurman, R.J and Ferenczy, A. . Precancerous Lesions of the Cervix. In: Kurman R.J. Blaustein's pathology of the female genital tract. Fifth Edition. New York. Springer-Verlag New York, Inc. 2001. p253-324