ANA MARIA DIAS FACHINI

FATORES DE RISCO PARA DIAGNÓSTICO HISTOLÓGICO DE LESÃO ESCAMOSA DE ALTO GRAU EM MULHERES COM RESULTADO CITOLÓGICO DE LESÃO DE BAIXO GRAU

RISK FACTORS FOR HISTOLOGICAL OUTCOME OF HIGH-GRADE LESIONS IN WOMEN WITH LSIL AS SHOWN BY SCREENING WITH CYTOLOGY

CAMPINAS
2015

UNIVERSIDADE ESTADUAL DE CAMPINAS
Faculdade de Ciências Médicas

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RISK FACTORS FOR HISTOLOGICAL OUTCOME OF HIGH-GRADE LESIONS IN WOMEN WITH LSIL AS SHOWN BY SCREENING WITH CYTOLOGY

Dissertação apresentada à Pós-Graduação em Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção do Título de Mestre em Ciências da Saúde, área de concentração em Oncologia Ginecológica e Mamária

Dissertation submitted to the Programme of Obstetrics and Gynecology of the Unicamp's Faculdade de Ciências Médicas for obtaining the title of MD in Health Sciences in the concentration area of Gynecologic Oncology and Mammary

ORIENTADOR: PROF. DR. LUIZ CARLOS ZEFERINO

ESTE EXEMPLAR CORRESPONDE À VERSÃO FINAL DA DISSERTAÇÃO DEFENDIDA PELA ALUNA ANA MARIA DIAS FACHINI E ORIENTADA PELO PROF. DR. LUIZ CARLOS ZEFERINO

Assinatura do **Orientador**

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CAMPINAS
2015

Ficha catalográfica
Universidade Estadual de Campinas
Biblioteca da Faculdade de Ciências Médicas
Maristella Soares dos Santos - CRB 8/8402

F118f

Fachini, Ana Maria Dias, 1980-
Fatores de risco para diagnóstico histológico de lesão escamosa de alto grau em mulheres com resultado citológico de lesão de baixo grau / Ana Maria Dias Fachini. – Campinas, SP : [s.n.], 2015.

Orientador: Luiz Carlos Zeferino.
Dissertação (mestrado) – Universidade Estadual de Campinas, Faculdade de Ciências Médicas.

1. Neoplasia intraepitelial cervical. 2. Programas de rastreamento. 3. Papillomaviridae. 4. Idade. I. Zeferino, Luiz Carlos,1955-. II. Universidade Estadual de Campinas. Faculdade de Ciências Médicas. III. Título.

Informações para Biblioteca Digital

Título em outro idioma: Risk factors for histological outcome of high-grade lesions in women with LSIL as shown by screening with cytology
Palavras-chave em inglês:
Cervical intraepithelial neoplasia
Mass screening
Papillomaviridae
Age
Área de concentração: Oncologia Ginecológica e Mamária
Titulação: Mestra em Ciências da Saúde
Banca examinadora:
Luiz Carlos Zeferino [Orientador]
Fábio Bastos Russomano
Luis Otávio Zanatta Sarian
Data de defesa: 04-08-2015
Programa de Pós-Graduação: Tocoginecologia

Diagramação e Revisão: Assessoria Técnica do CAISM (ASTEC)

BANCA EXAMINADORA DA DEFESA

ANA MARIA DIAS FACHINI

ORIENTADOR: PROF. DR. LUIZ CARLOS ZEFERINO

MEMBROS:

1.

2.

3.

Programa de Pós-Graduação em Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas

Data: 04 / 08 / 2015

RESUMO

Objetivo: Avaliar se há associação entre a idade da mulher ao diagnóstico, idade do início da atividade sexual (IAS), tempo de atividade sexual (TAS) e adimplência ao rastreamento do câncer do colo do útero em mulheres com resultado citológico de Lesão intraepitelial escamosa de baixo grau (LIE-BG) com o diagnóstico histológico final de Neoplasia Intraepitelial Cervical (NIC) 2 ou 3. **Método:** Este foi um estudo de corte transversal que incluiu 791 mulheres com LIE-BG no rastreamento do câncer do colo do útero. As variáveis analisadas foram fornecidas pelas mulheres no momento da admissão e anotadas no prontuário médico. As mulheres foram classificadas em adimplentes ou inadimplentes com o rastreamento do câncer do colo do útero de acordo as recomendações atuais vigentes para o Sistema Único de Saúde. **Resultados**: As mulheres com maior tempo TAS mostraram maior prevalência de NIC 3 (p=0,01). A IAS não revelou diferenças significativas para quaisquer dos desfechos analisados. As mulheres inadimplentes com o rastreamento mostraram maior prevalência de NIC 3 (p=0,008). As mulheres com 30 anos ou mais de idade e inadimplentes com o rastreamento do câncer do colo do útero têm mais chance de desenvolverem NIC 3 (OR=3,12; IC 95% 1,07-9,05); entretanto, essa significância torna-se limítrofe quando se incluem mulheres a partir dos 25 anos de idade (OR=2,44; IC 95% 0,99-5,99). Na análise multivariada, as mulheres com TAS $\geq$ 10 anos têm mais chance de revelar NIC 3 em relação àquelas com TAS $\leq$ 4 anos (OD=8,33; IC

95% 1,82-33,33) e àquelas com TAS entre 5 e 9 anos (OD=7,69; IC 95% 1,85-33,33). Em relação à adimplência com o rastreamento, os resultados apontam para maior chance de NIC 3 no grupo inadimplente, apesar da significância limítrofe (OD=2,39; IC 95% 0,96-5,92). Nenhuma associação foi encontrada para NIC 2 ou NIC 3 e para apenas NIC 3 em relação ao grupo etário e à IAS. **Conclusões:** As mulheres com exame citológico realizado para o rastreamento do câncer do colo do útero com resultado de LIE-BG têm maior probabilidade de apresentar o diagnóstico histológico de NIC 3 quando tiverem mais de dez anos de tempo de atividade sexual e quando forem inadimplentes com o rastreamento. A associação destas variáveis com o diagnóstico de NIC 3 estaria presente em mulheres com 30 anos ou mais.

Palavras-chave: neoplasia intraepitelial cervical, programas de rastreamento, papilomavírus humano, idade.

ABSTRACT

Objectives: This study aimed to evaluate if there is association between the woman´s age, age of first sexual intercourse (FSI), interval sine FSI and compliance with cervical cancer screening in women with Low-grade squamous intraepithelial lesion (LSIL) as shown by screening with cytology Cervical Intraepithelial Neoplasia (CIN) 2 or CIN 3 as the final outcome. **Methods:** This was a cross-sectional analysis with 791 women who showed LSIL by screening with cytology. The variables analized were obteined from women at the moment of admission and were written in the medical records. Women were classified as compliant and noncompliant with cervical cancer screening according to current brazilian recomendations. **Results**: Women with higher interval since FSI showed higher prevalence of CIN 3 (p=0.01). Age of FSI didn´t reveal significant statistical differences for any outcomes. Noncompliant women revealed higher prevalence of histological CIN 3 cases (p=0.008). Women aged 30 years or older and non-compliant with cervical cancer screening have more chance to develop CIN 3 (OR= 3.12; CI 95% 1.07-9.05), however, the significance becomes borderline if the analysis include women since 25 years old (OR=2.44; CI 95% 0.99-5.99). In the multivariate analysis, women with 10 years or more of interval since FSI have more chance to reveal develop CIN 3 in relation to those with four years or less (OD= 8.33; CI 95% 1.82-33.33) as to those with 5-9 years of interval since FSI (OD= 7.69; CI 95% 1.85-33.33). According to screening compliance, the results point to

higher chance of CIN 3 in the non- compliant group, although with borderline significance (OD= 2.39; CI 95% 0.96-5.92). No association was observed for CIN 2 or CIN 3 and only CIN 3 with age-group and age of FSI. **Conclusions:** Women with LSIL as shown by screening with cytology have higher probability to reveal CIN 3 outcome when they have 10 or more years of since FSI and when they are noncompliant with cervical cancer screening. The association between these variables would be present in women with 30 years old or more.

Keywords: cervical intraepithelial neoplasia, mass screening, human papillomavirus, age.

SUMÁRIO

AGRADECIMENTOS

Ao Prof. Dr. Luiz Carlos Zeferino, brilhante orientador, pela dedicação e por ter me acolhido como sua aluna.

Ao Marcelo, pela análise estatística.

A todas as pacientes que participaram deste estudo, meu reconhecimento, profundo respeito e gratidão.

À amiga Juliana, pelo apoio e parceria de todos esses anos.

Às minhas avós Maria Rosa e Iracema, exemplos de vida e de bondade.

Aos meus pais Valdir e Magali, que, em meio a tantas adversidades, não pouparam esforços para que eu tivesse acesso à educação de qualidade e chegar onde estou hoje. Muito obrigada!

Para ser grande, sê inteiro: nada

Teu exagera ou exclui.

Sê todo em cada coisa. Põe quanto és

No mínimo que fazes.

Assim em cada lago a lua toda

Brilha, porque alta vive.

Ricardo Reis

(heterônimo de Fernando Pessoa)

“O homem não pode se tornar um verdadeiro homem senão pela educação”

(Immanuel Kant)

SIGLAS E ABREVIATURAS

CEP – Comitê de Ética em Pesquisa

CI – *Confiance interval*

CIN – *Cervical intraepithelial neoplasia*

DTG – Departamento de Tocoginecologia

FSI – *First sexual intercourse*

HM-CAISM – CAISM: Hospital da Mulher Prof. Dr. José Aristodemo Pinotti - Centro de Atenção Integral à Saúde da Mulher

HPV – Papilomavírus humano

IAS – Idade de início de atividade sexual

IC – Intervalo de confiança

LIE-AG – Lesão intraepitelial escamosa de alto grau

LIE-BG – Lesão intraepitelial escamosa de baixo grau

LSIL – *Low-grade squamous intraepithelial lesion*

NIC – Neoplasia intraepitelial cervical

OR – *Odds Ratio*

TAS – Tempo de atividade sexual

UNICAMP – Universidade Estadual de Campinas

INTRODUÇÃO GERAL

No mundo, o câncer do colo do útero é o terceiro tipo de tumor mais diagnosticado na população feminina, estando atrás apenas dos cânceres de mama e colorretal. É a quarta causa mais frequente de óbito por câncer nesta população, atrás dos cânceres de pulmão, mama e colorretal. Para o ano de 2012, a estimativa foi de 527.624 casos novos da doença no mundo, com 265.672 mortes, sendo que 87% desses óbitos ocorreram em países em desenvolvimento (1).

A estimativa para o ano de 2014, no Brasil, foi de 15.590 casos novos dessa doença, correspondendo a 5,7% dos cânceres incidentes na população feminina, com um risco estimado de 15,33 casos a cada 100 mil mulheres por ano. Exceto pelos tumores de pele não-melanoma, o câncer do colo do útero é o mais incidente na região Norte (23,57/100 mil). Nas regiões Centro-Oeste (22,19/100 mil) e Nordeste (18,79/100 mil) é o segundo mais frequente. Na região Sudeste (10,15/100 mil), o quarto e, na região Sul (15,87/100 mil), o quinto mais frequente (2).

Trata-se de um importante problema de saúde pública no mundo porque é a doença neoplásica maligna mais evitável. Mais de 85% dos casos e mortes pela doença ocorrem em países em desenvolvimento, onde sua incidência é cerca de duas vezes maior, grande parte por conta da inexistência ou ineficácia de programas de rastreamento populacional (3, 4).

Sabe-se que o câncer do colo do útero desenvolve-se a partir de lesões precursoras induzidas pela infecção causada pelo papilomavírus humano (HPV), essencial para o seu desenvolvimento (5) e que é precedido por um longo período de doença pré-invasiva, denominada Neoplasia intraepitelial Cervical (NIC). Assim, a detecção e o tratamento precoces destas lesões são fundamentais para a prevenção do câncer do colo do útero, o que é factível através da coleta de esfregaço cervical para avaliação citológica, como propuseram Papanicolaou e Traut em 1943 (6).

Atualmente, a nomenclatura adotada para a descrição dos achados citológicos no Brasil baseia-se no Sistema Bethesda, que foi revisada e atualizada em 2001 e emprega os termos lesão intraepitelial escamosa de baixo grau (LIE-BG) e lesão intraepitelial escamosa de alto grau (LIE-AG), entre outros (7). Para os exames histopatológicos é utilizada a nomenclatura de Richart, a qual emprega os termos NIC 1, NIC 2, NIC 3 e carcinoma invasor (8). Importante ressaltar que a citologia oncológica é um exame presuntivo. O diagnóstico de NIC deve ser histológico e isso é obtido através de biópsia do colo uterino guiada por colposcopia ou através de conização, seja esta a bisturi ou com alça diatérmica.

Entretanto, a infecção pelo HPV, por si só, não é causa suficiente para o surgimento das lesões precursoras. O tipo e carga viral do HPV, fatores ligados à imunidade da paciente, sua genética, uso de contraceptivo oral, comportamento sexual e, ainda, o tabagismo parecem influenciar na persistência dessa infecção e no desenvolvimento e regressão dessas lesões (9).

A idade é outro fator muito importante, pois mulheres abaixo de 30 anos apresentam altos índices de regressão da doença, ao passo que a persistência da

infecção e evolução da doença são mais comuns acima deste grupo etário, em população não rastreada (10, 11).

A NIC 1, atualmente não é considerada lesão precursora do câncer do colo do útero, pois a análise da expressão dos genes do HPV segue um padrão de replicação viral sem hiperexpressão das oncoproteínas virais E6 e E7, como também a taxa de regressão espontânea desta lesão é elevada (11-14). As NIC 2 e NIC 3 seriam as verdadeiras lesões precursoras, uma vez que sua presença estaria associada à instabilidade genética da célula por hiperexpressão das oncoproteínas E6 e E7 do HPV.

Um ensaio clínico randomizado entre Brasil e Canadá comparou a eficácia entre seguimento clínico e tratamento imediato de mulheres com diagnóstico de NIC 1. A conclusão foi que a progressão para NIC 2, NIC 3 ou câncer dentro de 18 meses foi similar nos dois grupos, mostrando o caráter associado mais à infecção e menos com a instabilidade genética da célula comprometida (15).

Assim, os protocolos atuais não recomendam tratamento imediato em mulheres com diagnóstico histológico de NIC 1 (16-21). Duas condutas têm sido adotadas para as mulheres apresentando LIE-BG. A primeira é encaminhar todas as mulheres para avaliação colposcópica e a segunda é repetir o exame citológico após seis meses. O equívoco que se pode cometer com a segunda conduta é retardar o diagnóstico de uma NIC 3 ou lesão mais grave.

As recomendações atuais do Sistema Único de Saúde brasileiro orientam repetir o exame citológico após seis meses para as mulheres com resultado citológico de LIE-BG. Estas recomendações indicam que o início do rastreamento deve ser, nas mulheres que já tiveram relação sexual, a partir de 25 anos de

idade, e, após duas citologias consecutivas negativas com intervalo de um ano, o rastreamento pode ser realizado a cada três anos. As coletas devem seguir até a idade de 64 anos e serem interrompidas quando, após essa idade, as mulheres tiverem pelo menos dois exames negativos consecutivos nos últimos cinco anos (22).

Com base nisso, pode-se considerar uma mulher com até 25 anos de idade como adimplente com o rastreamento porque não precisa realizá-lo. Também são consideradas adimplentes as mulheres com intervalo, desde a última coleta de citologia, menor ou igual a três anos ou quando a primeira coleta de citologia é realizada até a idade de 26 anos. Em oposição, estaria inadimplente com o rastreamento a mulher que tem mais de 25 anos de idade e com intervalo desde o último rastreamento maior ou igual a 4 anos, ou quando a mesma realiza a primeira coleta de citologia com idade maior ou igual a 27 anos.

O fato de a NIC 1 ser uma lesão cuja prevalência é maior em mulheres jovens, inversamente ao que ocorre com a NIC 3 em mulheres não rastreadas, sugere que as mulheres mais velhas, entre a quinta e sexta décadas de vida e que apresentam citologia cervical alterada, mesmo que indicativa de LIE-BG, poderiam estar sujeitas a um maior risco de portar NIC 2 ou NIC 3.

Assim, as recomendações vigentes não consideram a idade, a IAS e o histórico de rastreamento para mulheres com LIE-BG. Sobre esta questão, pode-se admitir a hipótese de que um resultado citológico de LIE-BG em mulheres com citologias prévias negativas poderia permitir conduta expectante, ao passo que o mesmo resultado em mulheres mais velhas e inadimplentes com o rastreamento talvez mereça investigação imediata. Portanto, os resultados deste estudo visam a

identificar eventuais fragilidades na adoção da conduta expectante para a abordagem da mulher com exame citológico de LIE-BG.

OBJETIVOS

Objetivo Geral

Analisar se a idade da mulher, idade de início de atividade sexual, tempo de atividade sexual e adimplência ao rastreamento do câncer do colo do útero seriam fatores de risco para o diagnóstico histológico final de NIC 2 ou NIC 3 em mulheres com resultado citológico de LIE-BG.

Objetivos Específicos

- Verificar se há associação entre a prevalência do diagnóstico histológico de NIC 2 ou NIC 3 com a idade ao diagnóstico, idade de início de atividade sexual e o tempo de atividade sexual da mulher.
- Verificar se há associação entre a prevalência do diagnóstico histológico de NIC 2 ou NIC 3 com a adimplência ao rastreamento citológico para detecção do câncer do colo do útero.
- Testar se idade, idade de início da atividade sexual, tempo de atividade sexual e adimplência ao rastreamento do câncer do colo do útero teriam associação de risco com o diagnóstico histológico de NIC 2 ou NIC 3.

CAPÍTULO

Submission Confirmation

International Journal of Gynecology & Obstetrics (ijgo@figo.org)
Adicionar aos contatos
20/06/2015

Para: luiz.zeferino@gmail.com, anafachini@hotmail.com

06-20-2015

Luiz Carlos Zeferino,

Cidade Universitária Zeferino Vaz
Campinas
BRAZIL

luiz.zeferino@gmail.com;anafachini@hotmail.com

Dear Prof. Zeferino:

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Risk factors for histological outcome of high-grade lesions in women with LSIL as shown by screening with cytology

Abstract

Objectives: Low-grade squamous intraepithelial lesion (LSIL) has a higher prevalence in young women and conservative management should be considered apart from human papillomavirus testing. Women with LSIL cytology may have CIN2 or CIN3. Therefore, women with a higher risk for more severe lesions should be identified. This study aimed to evaluate the association of various factors with the histological outcome of women showing cytological LSIL. Methods: This study included 791 women who showed LSIL by screening with cytology who were referred for immediate colposcopy. The final diagnosis was considered as "no neoplasia" for 235 women who had normal colposcopy. The other 92 women underwent excision of the transformation zone. The variables analized were: woman's age, age of first sexual intercourse (FSI), the interval since FSI, and screening compliance. Results: A higher interval since FSI was associated with a higher prevalence rate for CIN3 and lower prevalence rates for no neoplasia and CIN1. No screening compliance was associated with a higher prevalence of CIN3 (OR=2.91; 95% CI 1.27–6.63). Multivariate analysis showed that the outcome for CIN3 was strongly associated with an interval $\geq$10 years since FSI taking as a reference $\leq$4 years (OR=8.33; 95% CI 1.82–33.33) and 5–9 years (OR=7.69; 95% CI 1.85–33.33), and it showed borderline association with no screening compliance (OR=2.39; 95% CI 0.96–5.92). The age of FSI was not associated with any diagnosis. Conclusions: Women with LSIL as shown by screening with cytology have a higher probability of occurrence of CIN3 if FSI was 10 or

more years ago and when they are noncompliant with cervical cancer screening. These women should have immediate colposcopy.

Introduction

CIN (Cervical Intraepithelial Neoplasia) 1 represents a productive infection by human papillomavirus (HPV) in the cervical epithelium. CIN2 and CIN3 are considered as the true precursor lesions of cervical carcinoma because of genetic cell instability by the action of E6 and E7 HPV oncoproteins. Therefore, it may progress to invasive disease (1-4).

The cytological result that corresponds to histological CIN1 is low-grade squamous intraepithelial lesion (LSIL). LSIL shows a higher prevalence in young women, when DNA-HPV testing has limited applicability. Therefore, more conservative management should be considered (5-10).

Women with LSIL as shown by cytology may show CIN2 or worse lesions. Therefore, women with the highest risk for more severe lesions should be identified. The ALTS (ASCUS LSIL Triage Study) was a randomized clinical trial that compared three different approaches for women with cytological results of atypical squamous cells of undetermined significance and LSIL: immediate colposcopy, DNA-HPV testing and follow-up with cytology (11). DNA-HPV was positive in 85% of the women with LSIL and then it does not fit well as triage for colposcopy. Referring all women for colposcopy might be excessive, mainly for younger women, because most of these lesions will regress (12).

A meta-analysis study on triage of women with LSIL showed a sensitivity of 92% for repeating cytology and a specificity of 42%. The Hybrid Capture 2 test showed a pooled sensitivity for CIN2+ of 95% and a specificity of only 33%. The sensitivity and specificity

ratios did not significantly differ from unity. On average, among women with LSIL, 17% have CIN2+ and 12% have CIN3+ (13-15).

Screening history, the woman's age, age of first sexual intercourse (FSI), and the interval since FSI are risk factors for neoplastic cervical lesions (16-19). The prevalence of CIN3 in screened women decreases for those older than 30 years, but this tendency is not observed in non-screened women (16). Therefore, this study aimed to evaluate the association of these risk factors with histological outcome of women showing cytological LSIL in cervical cancer screening.

Material and Methods

This study was a cross-sectional analysis that included 791 women showing LSIL by screening with cytology who were referred for colposcopy in the Woman's Hospital Prof. Dr. José Aristodemo Pinotti/CAISM of the State University of Campinas (UNICAMP), between January 2003 and March 2006. The data used in this study correspond to a period when all women with LSIL were referred for colposcopy. After this time, the guideline changed. The study protocol was previously approved by the institutional review board at UNICAMP and written informed consent was obtained from all of the enrolled patients.

The women included in this study were invited to participate in a randomized clinical trial, which compared expectant management versus immediate treatment for those with biopsy-proven CIN1 (20). Patients were excluded for any of the following reasons: unsatisfactory colposcopy; currently pregnant; prior therapy in the cervix; prior gynecological cancer; pelvic radiation; other malignancies; immunosuppressed because of

diseases, such as AIDS, organ transplantation, or use of immunosuppressive medications; and cognitively impaired or otherwise unable to provide written informed consent.

Cytological samples were obtained in the primary health care clinics of the Brazilian public health system for screening cervical cancer. All of the samples were analyzed in the Cytology Laboratory at the University. The assisting routine established that all women with LSIL by screening with cytology were referred for immediate colposcopy, and then a biopsy should be carried out when suspected image was detected. All of the biopsies were analyzed by the same pathologist from the Laboratory of Pathology of UNICAMP. The study end point was histological CIN2 or worse.

The screening history was classified as compliant and noncompliant according to Brazilian recommendations for cervical cancer screening, including the age group of 25 to 64 years old and a 3-year interval. Women were considered as compliant when one of the following parameters was present: younger than 25 years old (outside of the target age group); the interval since the last screening test was equal to or less than 3 years; and the first screening test was performed before 26 years old. Women were considered noncompliant when one of the following parameters was present: older than 25 years and the last screening test was performed at an interval greater than or equal to 4 years; and the first screening test was performed at an age older than 26 years. Data of the screening history were obtained from medical files.

For analysis, age was pooled into age groups: $\leq$24 years, 25–34 years, and $\geq$35 years. The age of FSI was pooled into $\leq$19 years and $\geq$20 years. The interval since FSI was calculated by subtracting the age of FSI from the woman's age at the moment of screening and was pooled into $\leq$4 years, 5–9 years, and $\geq$10 years. The age of women at the moment of screening and the age of FSI were obtained from the medical files.

Continuous variables were analyzed using analysis of variance for normal distribution of data or the Kruskal–Wallis test for non-normal distribution. For analysis of associations, the variables of the woman's age, age of FSI, interval since FSI, and screening compliance were grouped and analyzed as categorical variables. The association between two categorical variables was analyzed by the chi-square test. The magnitude of association between two categorical variables was estimated by odds ratios (ORs) with 95% confidence intervals (CIs). The association of independent variables with the outcome (dependent variable) was analyzed by logistic regression, and the results are expressed as ORs with 95% CIs. Statistical Analysis System (SAS) 9.2 for Windows was used for analysis.

Results

Table 1 shows the prevalence (%) of the final outcome according to the woman's age, age of FSI, interval since FSI, and cervical cancer compliance. According to age, older women had a higher prevalence of no neoplasia (p=0.002) but there was a lower prevalence of histological CIN1 (p=0.001). No significant difference in prevalence was observed for CIN2 and CIN3. The age of FSI, grouped as $\leq$19 and $\geq$20 years, did not affect any outcomes. According to the interval since FSI, women with a higher interval showed a higher prevalence of CIN3 (p=0.01) and non-neoplasia outcome (p=0.01). However, women with a higher interval since FSI showed a lower prevalence of CIN1 (p=0.001). Noncompliant women had a higher prevalence of histological CIN3 (p=0.008). However, compliant women showed a higher prevalence of histological CIN1 (p=0.002). Figure 1 shows the positive predictive value for CIN2 and CIN3 according to age group, age of FSI, the interval since FSI, and screening compliance.

Women who were aged 30 years or older and were noncompliant with cervical cancer screening had a greater chance of developing CIN3 (OR=3.12; 95% CI 1.07–9.05), but this significance was borderline if the analysis included women younger than 25 years old (OR=2.44; 95% CI 0.99–5.99). No significant difference was observed in the histological outcome of CIN2 or CIN3 (Table 2).

In multivariate analysis, women who had an interval of 10 years or more since FSI had a greater chance of developing CIN3 compared with those with an interval of 4 years or less (OR=8.33; 95% CI 1.82–33.33) and those with an interval of 5–9 years since FSI (OR=7.69; 95% CI 1.85–33.33). According to screening compliance, there was a higher chance of CIN3 occurring in the noncompliant group, but this was borderline significant (OR=2.39; 95% CI 0.96–5.92). No association was observed for CIN2 or CIN3, except for CIN3 with the age group and age of FSI (Table 3).

Discussion

Our study showed that women with LSIL as shown by screening with cytology had a higher probability of having a histological outcome of CIN3 if they had a higher interval since their FSI and if they were noncompliant with cervical cancer screening. The prevalence rate of CIN3 increased as the interval since the FSI increased. Multivariate analysis showed that women with an interval of 10 years or more since FSI had a greater chance of occurrence of CIN3 compared with those with an interval of 4 years or less and those with an interval of 5–9 years since FSI. Previous studies have shown that CIN3 is related to persistence of high-risk HPV infection that was acquired some years ago and this risk increases with this interval (21, 22).

Similarly, no compliant women with screening showed a higher prevalence of CIN3, but multivariate analysis revealed borderline significance. For both variables, no significant differences were observed when CIN2 or worse was analyzed. Screening compliance was tested for women who were older than 25 years and older than 30 years. The association between screening compliance with histological CIN3 was significant for women aged 30 years or older, but the significance was borderline when women who were older than 25 years were analyzed. This finding suggested that the age group of 25–29 years did not have an increased chance of CIN3.

No significant association was observed for age of FSI and histological outcome, although this variable was analyzed in only two categories. We consider that most women have had their FSI at an age younger 20 years old, as observed in this study (663/752). Therefore, we considered that the remaining women had lately their FSI.

No significant association was also observed for the woman's age and histological outcome. Age was analyzed in three categories, which included women who were younger than 25 years old who are outside of the recommended age group for cervical screening in many worldwide guidelines. The interval since FSI is a combination of the age at diagnosis and age at FSI, and this represents the interval of risk to acquire a persistent HPV infection. The longer this interval is, the higher the risk for malignant transformation of the cervical epithelium (23).

The outcome of no neoplasia was more frequent in older and compliant women and it was not associated with the age of FSI. These findings could be explained by the higher percentage of compliant women (90.4%) that clearly prevented CIN3 in older women, and the prevalence of CN1 was higher in younger women. In fact, screening with cytology does not prevent CIN1 because this lesion is considered as morphological expression of transient

HPV infection, which is higher after the beginning of sexual intercourse, as shown in our study.

The outcome of CIN2 was not associated with any of the analyzed variables. This finding was unsurprising because this lesion might clinically resemble CIN1 or CIN3 (2). Expectant management of CIN2 in women showing LSIL by cytology showed a high rate of spontaneous regression, similar to that observed for CIN1 (24).

Therefore, repeating cytology before referring for colposcopy in women showing cytological LSIL could be appropriate if the interval since FSI is less than 5 years and for those women who are complaint for cervical cancer screening. This expectant management could be considered safe for these women, although they are noncompliant and younger than 30 years old. Otherwise, the chance of occurrence of CIN3 would be higher in these women.

An absence of data regarding HPV infection is a limitation of this study. A DNA-HPV test triage for referral for colposcopy in women with cytological LSIL and atypical squamous cells of undetermined significance is one of the current recommendations. However, for cytological LSIL, this management is controversial (11). The DNA-HPV triage is less effective for women who are younger than 30 years old because the prevalence of HPV infection is higher in this age group and the rate of HPV-positive LSIL could reach more than 80% (11).

In conclusion, this study shows that women with LSIL as shown by screening with cytology have a higher probability of showing the outcome of CIN3 when they have an interval of more than 10 years since FSI and when they are noncompliant with cervical cancer screening.

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Table 1. Prevalence of the outcome of women who were referred because of cytological LSIL according to age, age of first sexual intercourse, the interval since the first sexual intercourse, and cervical cancer compliance

	Outcome								
	No neoplasia		CIN 1		CIN 2		CIN 3		Total
Age-group	N	%	n	%	n	%	n	%	n (%)
≤24 years	190	49.74	139	36.39	40	10.47	13	3.40	382 (100)
25-34 years	150	60.73	61	24.70	22	8.91	14	5.67	247 (100)
≥35 years	101	62.35	40	24.69	10	6.17	10	6.17	162 (100)
Total	441	55.75	240	30.34	72	9.10	37	4.68	791 (100)*
χ^2 for Trend		p=0.002		p=0.001		p=0.09		p=0.20	
Age of FSI									
≤19 years	362	54.60	202	30.47	64	9.65	34	5.13	663 (100)
≥20 years	52	58.43	28	31.46	6	6.74	3	3.37	89 (100)
Total	414	55.05	230	30.59	70	9.31	37	4.92	752 (100)*
χ^2		p=0.50		p=0.84		p=0.38		p=0.47	
Interval since FSI									
≤4 years	105	50.48	77	37.02	20	9.62	6	2.88	208 (100)
5 - 9 years	97	50.00	67	34.54	25	12.89	5	2.58	194 (100)
≥10 years	210	60.52	85	24.50	25	7.20	26	7.49	347 (100)
Total	412	55.01	229	30.57	70	9.35	37	4.94	749 (100)*
$\chi^2$for Trend		p=0.01		p=0.001		p=0.20		p=0.01	
Screening compliance									
No	49	66.22	11	14.86	6	8.11	8	10.81	74 (100)
Yes	381	54.43	225	32.14	65	9.29	28	4.00	700 (100)
Total	430	55.56	236	30.49	71	9.17	36	4.65	774 (100)*
χ^2		p=0.05		p=0.002		p=0.74		p=0.008	

FSI: first sexual intercourse.

No neoplasia: included women without biopsy and those with benign biopsy.

One woman had the outcome of carcinoma who was older than 35 years, with an age of FSI younger than 19 years, an interval higher than 10 years since FSI, and was compliant with cervical cancer screening.

*Unknown data were not included in the analysis.

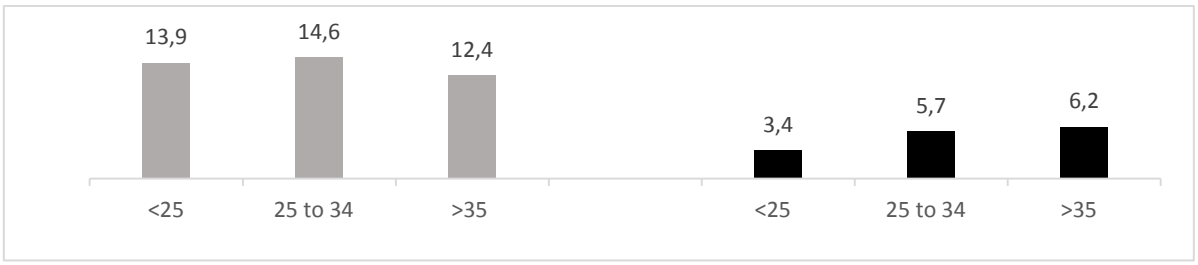
Table 2. Association of previous cervical cancer screening compliance and histological outcome for women who were referred because of cytological LSIL according to age group

Histological outcome	Screening compliance	≥25 years n/total cases (%)	≥30 years n/total cases (%)	All women n/total cases (%)
CIN 2 or CIN 3	No	14/74 (18.9)	8/47 (17.0)	14/74 (18.9)
	Yes	40/317 (12.6)	27/223 (12.1)	93/699 (13.3)
	OR (CI95%)	1.62 (0.83-3.16)	1.49 (0.63-3.52)	1.52 (0.82-2.83)
CIN 3	No	8/74 (10.8)	6/47 (12.8)	8/74 (10.8)
	Yes	15/317 (4.7)	10/223 (4.5)	28/699 (4.0)
	OR (CI95%)	2.44 (0.99-5.99)	3.12 (1.07-9.05)	2.91 (1.27-6.63)

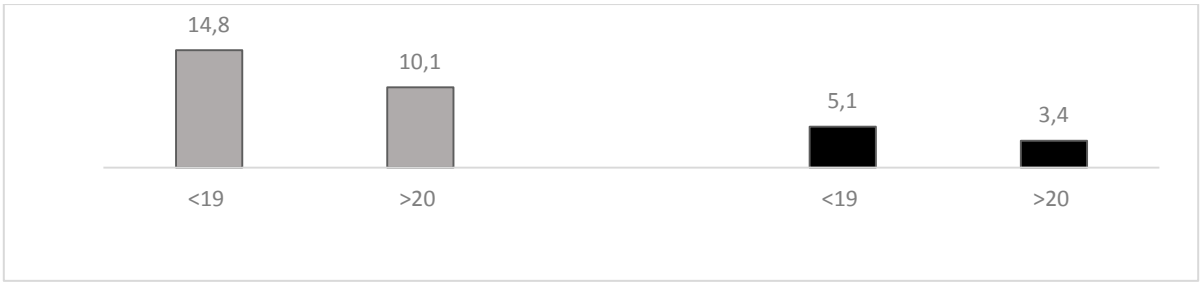
Table 3. Multivariate analysis for age at diagnosis, age of first sexual intercourse, interval since the first sexual intercourse, and screening compliance for CIN2 or CIN3 and the final outcome of CIN3

CIN 2 or CIN 3				
Variable	Categories			OR (IC 95%)
Age group	≥35	*vs*	25-34	1.10 (0.59-2.06)
	≥35	*vs*	<25	1.41 (0.50-3.96)
Age of FSI	≤19	*vs*	≥20	1.36 (0.63-2.95)
Interval since FSI	≥10	*vs*	≤4	1.47 (0.57-3.85)
	≥10	*vs*	5-9	1.13 (0.49-2.63)
Screening compliance	No	*vs*	Yes	1.57 (0.81-3.09)
CIN 3				
Variable	Categories			OR (IC 95%)
Age group	≥35	*vs*	25-34	1.01 (0.42-2.42)
	≥35	*vs*	<25	4.08 (0.91-18.32)
Age of FSI	≤19	*vs*	≥20	1.27 (0.36-4.48)
Interval since FSI	≥10	*vs*	≤4	8.33 (1.82-33.33)
	≥10	*vs*	5-9	7.69 (1.85-33.33)
Screening compliance	No	*vs*	Yes	2.39 (0.96-5.92)

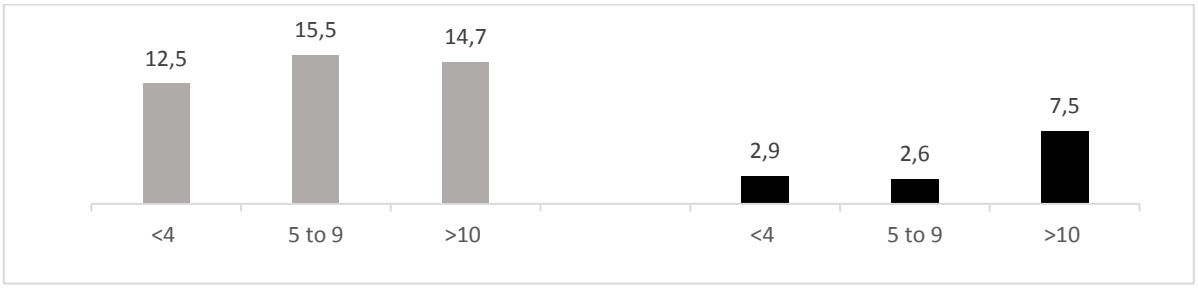
FSI: first sexual intercourse.



Age-group



Age of FSI



Interval since FSI

Screening compliance

Figure 1. Positive predictive value for CIN2 (gray bars) and CIN3 (black bars) according to age group, age of first sexual intercourse (FSI), interval since FSI, and screening compliance.

CONCLUSÃO GERAL

- Para mulheres com resultado citológico de LIE-BG, a prevalência do diagnóstico histológico de NIC 2 ou NIC 3 não variou com a idade da mulher ao diagnóstico e idade de início de atividade sexual. A prevalência de NIC 3 foi mais alta em mulheres com maior tempo de atividade sexual.
- As mulheres inadimplentes com o rastreamento do câncer do colo do útero apresentaram maior prevalência de NIC 3.
- As mulheres com exame citológico realizado para o rastreamento do câncer do colo do útero com resultado de LIE-BG têm maior risco de apresentar o diagnóstico histológico de NIC 3 quando tiverem mais de dez anos de tempo de atividade sexual e quando forem inadimplentes com o rastreamento.

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ANEXOS

Carta de aprovação do projeto no CEP

FACULDADE DE CIÊNCIAS MÉDICAS
COMITÊ DE ÉTICA EM PESQUISA

http://www.fcm.unicamp.br/fcm/pesquisa/comite-de-etica-em-pesquisa

CEP, 22/10/13.
(**PARECER CEP:** N° 023/2003)

PARECER

I – IDENTIFICAÇÃO:

PROJETO: **"ESTUDO RANDOMIZADO DE TRATAMENTO IMEDIATO VERSUS SEGUIMENTO COLPOSCÓPICO PARA PACIENTES COM NIC 1 COMPROVADO POR BIÓPSIA".**

PESQUISADOR RESPONSÁVEL: Luis Carlos Zeferino

II – PARECER DO CEP

O Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP tomou ciência e aprova o adendo que inclui o subprojeto **"DIAGNÓSTICO HISTOLÓGICO FINAL EM MULHERES COM RESULTADOS CITOLÓGICO DE LIE-BG EM FUNÇÃO DA IDADE, HISTÓRIA PRÉVIA DE RASTREAMENTO E COM EXTENSÃO E LOCALIZAÇÃO DA LESÃO NO COLO DO ÚTERO"**, com finalidade de mestrado da aluna Ana Maria Dias Fachini, referente ao protocolo de pesquisa supracitado.

O conteúdo e as conclusões aqui apresentados são de responsabilidade exclusiva do CEP/FCM/UNICAMP e não representam a opinião da Universidade Estadual de Campinas nem a comprometem.

III – DATA DA REUNIÃO.

Homologado na X Reunião Ordinária do CEP/FCM, em 22 de outubro de 2013.

Profa. Dra. Fátima Aparecida Böttcher Luiz
COORDENADORA do COMITÊ DE ÉTICA EM PESQUISA
FCM / UNICAMP

Comitê de Ética em Pesquisa - UNICAMP
Rua: Tessália Vieira de Camargo, 126
Caixa Postal 6111
13083-887 Campinas – SP

FONE (019) 3521-8936
FAX (019) 3521-7187
cep@fcm.unicamp.br

Carta de aprovação do projeto na Comissão de Pesquisa do DTG/CAISM

UNICAMP

Comissão de Pesquisa do DTG / CAISM

Campinas, 24 de setembro de 2013.

Protocolo nº: 066/2013

O protocolo de pesquisa *"Diagnóstico histológico final em mulheres com resultado citológico de LIE-BG em função da idade, história prévia de rastreamento e com extensão e localização da lesão no colo do útero"*, do pesquisador Ana Maria Dias Fachini, orientada pelo Prof. Dr. Luiz Carlos Zeferino, foi aprovado pela Comissão de Pesquisa do DTG/CAISM em 24/09/2013.

Atenciosamente,

PROF. DR. JOSÉ GUILHERME CECATTI
Presidente da Comissão de Pesquisa do DTG/CAISM

Rua Alexander Flemming, n.º101 – Cidade Universitária Zeferino Vaz – Campinas-SP
Fone: (19) 3521-9400
comissaopesquisa@caism.unicamp.br