

# Ruolo della biopsia in colposcopia e rischio di carcinoma invasivo

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# Disclosures

- No financial relationships or conflict of interest to disclose

# Background

- Colposcopy is used, among other things, to define which women need treatment to prevent an invasive cervical cancer
- A number of studies showed that, by performing random biopsies, some 20% more high-grade CIN are detected
- Only part of high-grade CIN progress to invasion and after long time (about 1/3 in 30 years for CIN3 Mc Credie et al Lancet Oncol 2007)
- Little is known about the risk of invasive cancer after a colposcopy according to colposcopy's and woman's features

# Objectives

1. Evaluating the ability of colposcopy to stratify women with abnormal cytology as for their risk to carry/ develop invasive cervical cancer.
2. Evaluate the relative protection of colposcopy with and without biopsy

# Setting

- Organized screening programme active from 1992
- Women with abnormal cytology ( $\geq$  ASC-US) referred for colposcopy in pre-defined centres (>80% attend)
- All cytologies registered
- All colposcopies (biopies taken and their result) registered
- Colposcopic impression registered but, to the moment, not used for computerised management of women
- Treatments registered
- Cancer Registry covering greater Turin active from 1980s

# Methods 1

- Women having had a first screening test before Dec 31 2012 included
- Women classified according to screening history and features of their first colposcopy
- Linkage with cancer register
- ICC incidence computed from t0 (group specific, see next table) to (a) end of follow-up (Dec,31,2012) or (b) date of death or emigration or (c) date of cancer diagnosis, whichever first.

# Methods 2

## A priori classification of women and t0

group

Never had abnormal cytology

Abnormal cytology ( $\geq$ ASC-US) but no colposcopy

Abnormal cytology, colposcopy(ies) without biopsy at the first

Abnormal cytology, colposcopy(ies) biopsies  $<$ CIN2 only at the first

Abnormal cytology, colposcopy(ies) with  $\geq 1$  biopsy(ies)  $\geq$ CIN2 at the first

t0

Date first cytology in screening programme

Date first abnormal cytology

Date first colposcopy

Date first colposcopy

Date first colposcopy

# Risk stratification

Is colposcopy with and without biopsy (and other variables) able to identify women who do not carry nor will develop invasive cancer?

- Reference

- Never abnormal cytology
- (Abnormal cytology, no colposcopy)

- Study groups:

- No biopsy (no suspect area should have been identified) low risk expected
- Negative biopsy (low risk expected)

- Cancers included

- All

- Confounding

- IRRs age-adjusted by Poisson regression (10-year groups)



# Protection

Does taking biopsies increase protection from cancer?

- **Comparison:** colposcopy with biopsy vs. colposcopy without biopsy
- **From which cancers?**
- All
- Cancers with CIN2/3 detected >6 months in advance excluded (failure of treatment or no treatment)
- Cancers diagnosed within 6 months of 1st colposcopy excluded (delayed recognition of need for colposcopy or colposcopy delayed )
- Both excluded (remaining are the cancers preventable by improving colposcopy/biopsy performance)

# Confounding

- Non-randomised study. Groups have different baseline cancer risk
- Adjusted relative cancer incidence (Poisson regression)
  - Age
  - Referral cytology HSIL or ASC-H

# Results 1

- 224,137 women included (median age 41 years, IQR 32-52)
- 5666 (2.5%) with at least one colposcopy
- 85.8% of them had at least 1 repeat repeat colposcopy. Median number of colposcopy repeats 3 (IQR 1-6)
- 2,401,514.03 years of follow-up (median 11.5, IQR 5.1-16.2).
- 37.4% of colposcopies had at least 1 biopsy
- 79.8% of women with colposcopy had at least 1 biopsy
- 1116 women detected to have CIN 2 or 3, 28.4% of whom after the first colposcopy.
- 149 ICC registered at Cancer Registry
- 26 (17.4%) of them diagnosed after a CIN2/3

## Risk stratification. All cancers included

	No women	Person-years	CA	Incidence Per 10,000	IRR vs. never abnormal cytology§
Never abnormal cytology	217,616	2,351,379.5	76	0.32	1
Abnormal cytology no colposcopy	855	8604.3	14	16.27	<b>58.92</b> (33.00-105.19)
Abnormal cytology 1st colposcopy without biopsy	1835	12,140.1	8	6.59	<b>20.07</b> (9.69-41.59)
Abnormal cytology 1st colposcopy with biopsy<CIN2	3269	26,157.1	5	1.91	<b>6.16</b> (2.49-15.23)

§ adjusted for age (10-yr groups) by Poisson regression

Risk stratification. All cancers included  
 Detail women with 1st colposcopy without biopsy

	No women	Person-years	CA	Incidence Per 100,000	IRR vs. never abnormal cytology§
1st colposcopy without biopsy grading<2 and referral cytology not HSIL/ASC-H	1789	11,932.82	4	3.35	<b>10.29</b> (3.77-28.13)
1st colposcopy without biopsy, grading≥2	12	32.49	1	307.8	<b>973.79</b> (133.22-7118)
1st colposcopy without biopsy, grading<2 and referral cytology ≥HSIL/ASC-H	34	174.81	3	171.6	<b>479.91</b> (150.51-1530)

§ adjusted for age (10-yr groups) by Poisson regression

# Risk stratification. All cancers included

## Detail women with 1st colposcopy without biopsy

Women with 1st colposcopy grade not reported or unsatisfactory excluded

	No women	Person-years	CA	Incidence Per 100,000	IRR vs. never abnormal cytology§
1st colposcopy without biopsy grading<2 and referral cytology not HSIL/ASC-H	1267	7703.67	3	3.89	<b>11.15</b> (3.52-28.13)
1st colposcopy without biopsy, grading<2 and referral cytology ≥HSIL/ASC-H	19	64.56	3	464,68	<b>843.53</b> (206.29-1530)

§ adjusted for age (10-yr groups) by Poisson regression

# Conclusions risk stratification

- Cancer occurrence (both prevalence and incidence) in women with **abnormal cytology and no colposcopy** very high
- With **colposcopy but no biopsy** cancer incidence about 1/3 that without colposcopy but 20 fold that in women with always normal cytology
- With **negative biopsy** cancer incidence about 1/10 that without colposcopy but 6 fold that in women with always normal cytology.
- **HSIL cytology strong risk predictor**. Consider diagnostic LLETZ if no abnormal area seen.
- When excluding a few women with colposcopy grade  $\geq 2$  and those with cytology ASC-H or HSIL, risk of women with colposcopy but no biopsy 1/6 that without colposcopy but still 1.7 fold that of women with negative biopsy and 10 fold that in women with always normal cytology.

- Colposcopy alone is largely imperfect in identifying, among women with abnormal cytology, those at low risk of carrying or developing invasive cancer



# Protection

# Invasive cancers in women who had colposcopy for cytology ASC-US+

	All cancers	Cancers not preceded by CIN2/3 (or detected within 6 months of previous CIN2/3) <b>Potentially preventable by identifying CIN2+</b>	Cancers detected >6 months of t0 <b>Plausibly not yet present at 1° colposcopy</b>	Cancers with no previous CIN2/3 (or within 6 months of previous CIN2/3) and detected >6 months of t0
Colposcopy	63	52 (88%)	15 (25%)	8 (13.5%)
First colposcopy with biopsy	51	44	10	3
First colposcopy without biopsy	8	8	5	5
- No eventual biopsy	5	5	5	5
- Eventual biopsy	3	3	0	0

# Invasive cancers in women who had colposcopy

- Only 13.5% of the cancers occurring at/after 1st colpo potentially preventable by improving colposcopy performance
  - 12% occurring >6 mths after HCIN detection (delayed treatment, treatment failure/recurrence)
  - Of the remaining 88%, 74.5% occurred within 6 months of t0. Plausibly already there. Delayed recognition that colposcopy was needed or delayed performance of colposcopy.

# Relative cancer incidence. Women without vs. women with biopsy at first colposcopy

	All cancers and person-years included	Only cancers with no previous CIN2/3 (or within 6 months of previous CIN2/3)	Cancers and person-years within 6 months of t0 excluded	Only cancers with no previous CIN2/3 (or within 6 months of previous CIN2/3) Cancers and person-years within 6 months of t0 excluded
Adjusted age	0.35 (0.17-0.75)	0.41 (0.19-0.86)	1.18 (0.40-3.49)	3.88 (0.92-16.37)
adjusted age§ and referral because cytology ASC-H or HSIL+	<b>1.23</b> (0.54-2.79)	<b>1.68</b> (0.73-3.86)	<b>2.81</b> (0.81-9.68)	<b>16.82</b> (3.29-85.9)

## Relative cancer incidence. Women without vs. women with biopsy at first colposcopy

	All cancers and person-years included	Only cancers with no previous CIN2/3 (or within 6 months of previous CIN2/3)	Cancers and person-years within 6 months of t0 excluded	Only cancers with no previous CIN2/3 (or within 6 months of previous CIN2/3) Cancers and person-years within 6 months of t0 excluded.
Exposed: women who had no biopsy after 1° colposcopy	<b>1.70</b> (0.65-4.47)	<b>2.28</b> (0.86-6.06)	<b>6.48</b> (1.93-21.7)	<b>35.10</b> (7.02-175.5)
Exposed: women who had ≥1 biopsy after 1° colposcopy	<b>0.82</b> (0.24-2.80)	<b>1.20</b> (0.34-4.18)	--	--

adjusted age, referral because cytology ASC-H or HSIL+

# Conclusions on protection

- Small number of cancers preventable by improving colposcopy/biopsy performance
- For such cancers risk significantly increased in women who had no biopsy during colposcopies
- Overall risk for such cancers significantly increased also in women who had no biopsy at 1st colposcopy
- No such cancer in women who had biopsy after first colposcopy

# Credits

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