Clinical outcomes after conservative management of CIN1/2, CIN2, and CIN2/3 in women ages 21-39 years

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Management of Abnormal Results

- ASCCP Guidelines[1]:
  - When **CIN3** is found in women of **any age**, treatment is recommended
  - When **CIN2/3** is found in young women, observation or treatment is acceptable
  - When **CIN2** is found in **young women**, observation is preferred but treatment is acceptable

- Conservative management = intensive observation/repeated testing instead of immediate treatment
  - Monitor for regression vs progression

[1]*Massad et al. JLGTD 2013*

Study Aim

Assess clinical outcomes among younger women (ages 21-39 years) with conservatively managed CIN2

Kaiser Permanente Northern California (KPNC)

- NCI Collaboration: following over 1 million women in cervical cancer screening since 2003

Large integrated healthcare system

- 2003: began cotesting with 3-year screening intervals
- 2007: implemented HPV vaccination

- Demonstration project of real world clinical effectiveness

Study Population

Women ages 21-39 enrolled at KPNC since 2003

- First abnormal biopsy result of CIN1/2, CIN2, CIN2/3 (baseline histology)
- Not immediately referred for treatment (no treatment for >4 months after abnormal result)
- Remained in KPNC for cervical cancer screening for at least 22 months after histology result

2,417 women included

- Median follow-up: 48 month (IQR: 31-71 months)

Outcome Definitions

Outcome Category	Definition
1. Progressed to cancer	Cancer histology from biopsy or treatment
2. Treated	LEEP (loop electrocautery excision procedure
	Cold knife cone (cone biopsy)
	Hysterectomy
3. Return to routine screening	2 negative cytologies and/or colposcopies at 6 and 12 months AND negative cotest at 24 months
4. Persistent high grade lesion	CIN2/3/AIS detected at LEEP
	CIN2/3/AIS detected at biopsy without subsequent regression
5. Persistent low grade lesion	Remaining women who did not fit into 4 groups above. All had at least 1 abnormal biopsy, HPV or Pap test

Baseline histology results

	Total	Age 21-24	Age 25-29	Age 30-34	Age 35-39
	%	%	%	%	%
Total (N)	2417	757	848	556	256
CIN1/2	17.7	18.1	15.3	22.1	17.2
CIN2	69.0	71.2	71.1	65.5	64.0
CIN2/3	13.2	11.6	13.6	12.4	18.8

Majority of results are CIN2

Somewhat higher CIN2/3, lower CIN2 for older age groups

Clinical outcomes by baseline diagnosis

	Baseline histology				
	Total		CIN1/2	CIN2	CIN2/3
	N	%	%	%	%
Total (N)	2417	100	428	1670	319
Cancer	6	0.3	0.2	0.2	0.6
Treated	717	29.7	23.1	30.0	37.0
Exit colposcopy	474	19.6	21.5	18.3	24.1
High-grade lesion	172	7.1	7.9	7.2	5.6
Low-grade lesion	1048	43.4	47.2	44.4	32.6

- Treatment increased with worse disease
- Less than 20% exited colposcopy
- Half remained in follow-up
  - 55% of CIN1/2
  - 51% CIN2
  - 38% CIN2/3
- Low-grade persistence highest in CIN1/2 and CIN2

Clinical outcomes by age

	Total		Age 21-24	Age 25-29	Age 30-34	Age 35-39
	N	%	%	%	%	%
Total (N)	2417	100	757	848	556	256
Cancer	6	0.3	0	0.4	0.4	0.4
Treated	717	29.7	25.5	32.3	29.5	33.6
Exit colposcopy	474	19.6	16.1	17.7	23.7	27.3
High-grade lesion	172	7.1	9.5	7.9	4.5	3.1
Low-grade lesion	1048	43.4	48.9	41.8	41.9	35.6

- Higher treatment among older women and more exit colposcopy
- Low-grade persistence in half of women under 25

Screening history of cancer cases

Case 1: 2 year gap from CIN2 to next visit where cone biopsy detected SCC

Case 2: 2 year gap from CIN1/2 to next visit where HPV+/HSIL led to cone biopsy and detection of SCC

Case 3: 3 year gap from CIN2 to next visit where HPV+/HSIL led to cone biopsy and detection of SCC

Case 4: Sequential HPV+ cotests led to biopsy which detected SCC

Case 5: CIN2 biopsy led to LEEP which detected microinvasive SCC

Case 6: Persistent HPV+ and then HSIL led to LEEP which detected microinvasive SCC

- All cancers were preceded by at least 1 high-grade abnormal result (CIN2+ or HSIL) and/or patient failure to return
- No cancers after negative co-test

Conclusions

- 30% of women required treatment in the future (esp. CIN2/3, age 35+)
- No cancers occurred after a negative cotest
- Less than 20% met criteria to exit intensive follow-up despite average of 4 years of follow-up
- 40-60% remained in intensive colposcopy protocol in the absence of continued CIN2+
  - Failure to ‘clear’ or return to normal, but no progression either
  - Continued cycle frequent tests

Interpretation and clinical relevance

- Prolonged surveillance is required to return to routine screening in the absence of continued CIN2+, many women fall into this category
- How can we identify which women can return to routine screening after fewer follow-ups without increasing cancer risk?
  - Age? Genotype? Other markers?
- How can we review clinical practices guidelines to better target which women need follow-up?

Questions?

KPNC Post-biopsy Guidelines: CIN1/2

- Summary: management depends on age and preceding Pap result

- After HPV-positive ASCUS, LSIL or sequential HPV positive
  - Ages 21-24: retest in 12 months
  - Ages 25+: retest in 12 months; CIN1/2 may be followed indefinitely or treated after at least 24 months of follow-up
- After ASC-H or HSIL
  - Ages 21-24: Observation with colposcopy and cytology at 6 month intervals for up to 24 months
  - Ages 25+: Diagnostic excisional procedure or cotesting at 12 and 24 months
- CIN1/2 should not be treated in women 21-24 regardless of prior Pap result

KPNC Post-biopsy Guidelines: CIN2 or CIN2/3

Ages 21-24: Observation with colposcopy and cytology at 6 month intervals for at least 12 months, up to 24 months

Ages 25+: Excision preferred if childbearing complete; observation as described above if childbearing not completed

Treat if CIN2+ persists at 24 months

Caveat: Manage appropriate to age, reproductive ambitions, and histology, and patient preference

KPNC Post-biopsy Guidelines: CIN3

Immediate precursor to invasive cancer and should be treated regardless of age or reproductive concerns

‘Observation is unacceptable if cancer prevention is the goal’