

# Pap Smears in the Diagnosis of Cervical Cancer: Help or Hinder?

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## Disclosures

• No financial relationships or conflict of interest to disclose



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## Introduction

- Cervical Cancer has a long natural history and can be present on the cervix for several years prior to diagnosis- several studies suggest a diagnostic preclinical phase of up to 7 years prior to confirmation of invasive disease (Rustagi et al <u>Am J Epidemiol</u>. 2014 May 1; 179(9): 1107–1114.)
- Stage IA cancer is microscopic; Stage IB-IV typically involve large tumors replacing the cervix and are always clinically apparent
- Symptoms of cervical tumors are abnormal bleeding, discharge, pain, etc
- Invasive cancers can be seen with the naked eye and have a very typical physical exam finding
- Cervical cancer is confirmed with a biopsy
- A pap smear is NOT a diagnostic tool for cervical cancer (other than microscopic disease) and will have a high false negative rate



## Introduction

 The purpose of this study is to evaluate the impact of performing a "diagnostic pap test" defined as done 0-2 years prior to a confirmation of cervical cancer to determine its impact on diagnosis and treatment of invasive disease that is likely already present on the cervix



## Methodology

#### **Inclusion criteria**

• Women diagnosed with invasive cervical cancer diagnosis between 2011 and 2014

#### Index pap test

- A pap test within 2 years of cervical cancer diagnosis date is considered a diagnostic test
- If there were two pap tests within the two years prior, the most recent pap test was used as the index pap test
- If a woman had colposcopy up to 7 days before her Pap test, an older pap test within the 2 year period was sought. If a previous pap test was identified, the pap test was considered the index pap

#### Data sources

- Ontario Cancer Registry (OCR) database → to identify cervical caner patients
- OHIP data → to identify colposcopy procedures
- Cytobase data  $\rightarrow$  to identify pap tests
- RPDB linked to OCR  $\rightarrow$  to identify patient characteristics
- Corporate Provider Database (CPDB)→ to identify provider characteristics



## Methodology

### **Patient Characteristics**

- Age
- Cancer Stage (IA, IB, II, III, IV)
- Histology (Adenocarcinoma, Squamous cell )
- Neighborhood income Quintile/ Residency
- PEM Status at diagnosis (Rostered, Not Rostered)
- Had Colposcopy between Index pap test and Diagnosis (Yes, No)
- Cytology result (AGC/AIS, HSIL/ASC-H, LSIL/ASCUS, Normal, Other, Squamous/Adenocarcinoma, Unknown)

### **Provider Characteristics**

- Gender
- Physician Specialty (Family Practice, OBGYN, Nurse, Other, Unknown)
- Provider location (Rural, Urban, Unknown)



# Methodology

## Analysis

- Demographic table of women stratified by those who received a diagnostic pap and those without
- Cytology results compared across stage of cervical cancer
- Median time between diagnosis and index pap compared across Cytology
  - Stratified by provider specialty
- Median time between diagnosis and index pap compared across cancer stage
  - Stratified by provider specialty and cytology

## Models

- Estimated effect of Age, Cancer stage and Histology on likelihood pap test result is normal or low grade
  - Univariate and multiple logistic regression
- Estimated effect of Age, Cancer stage, Income, PEM status and Histology on likelihood of having an index pap
  - Univariate and multiple logistic regression
- Estimated effect of Age, Cancer stage, Physician Specialty and Cytology result on likelihood of having a colposcopy
  - Univariate and multiple logistic regression



## Patient Demographic

Characteristics		Pap not performed N (%)	Pap Performed and Result known N (%)	Pap performed but result not known N(%)	All N (%)
Total		492 (100)	1250 (100)	260 (100)	2002 (100)
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Age group	21-69	354 (72)	1177 (94.2)	235 (90.4)	1766 (88.2)
	70+	138 (28)	73 (5.8)	25 (9.6)	236 (11.8)
	21-29	13 (2.6)	84 (6.7)	16 (6.2)	113 (5.6)
	30-39	52 (10.6)	309 (24.7)	48 (18.5)	409 (20.4)
	40-49	81 (16.5)	376 (30.1)	81 (31.2)	538 (26.9)
	50-59	114 (23.2)	256 (20.5)	50 (19.2)	420 (21)
	60-69	94 (19.1)	152 (12.2)	40 (15.4)	286 (14.3)
	70-79	76 (15.4)	51 (4.1)	16 (6.2)	143 (7.1)
	80+	62 (12.6)	22 (1.8)	9 (3.5)	93 (4.6)
Income Quintile	Q1	133 (27)	238 (19)	53 (20.4)	424 (21.2)
	Q2	73 (14.8)	224 (17.9)	35 (13.5)	332 (16.6)
	Q3	85 (17.3)	227 (18.2)	57 (21.9)	369 (18.4)
	Q4	77 (15.7)	222 (17.8)	43 (16.5)	342 (17.1)
	Q5	61 (12.4)	187 (15)	39 (15)	287 (14.3)
	Rural or Unknown	63 (12.8)	152 (12.2)	33 (12.7)	248 (12.4)



## Patient Demographic (2)

Characteristics		Pap not performed N (%)	Pap Performed and Result known N (%)	Pap performed but result not known N(%)	All N (%)
Total		492 (100)	1250 (100)	260 (100)	2002 (100)
Index Pap result	100/110			(0)	404 (07)
	AGC/AIS	(0)	194 (15.5)	(0)	194 (9.7)
	HSIL/ASC-H	(0)	657 (52.6)	(0)	657 (32.8)
	LSIL/ASCUS	(0)	103 (8.2)	(0)	103 (5.1)
	Normal	(0)	163 (13)	(0)	163 (8.1)
	Other Squamous/	(0)	40 (3.2)	(0)	40 (2)
	Adenocarcinoma	(0)	93 (7.4)	(0)	93 (4.6)
	Unknown	492 (100)	(0)	260 (100)	752 (37.6)
Any colposcopy	No	375 (76.2)	331 (26.5)	123 (47.3)	829 (41.4)
	Yes	117 (23.8)	919 (73.5)	137 (52.7)	1173 (58.6)
	I	114 (27)	737 (68.6)	122 (55.7)	973 (56.7)
		82 (19.4)	157 (14.6)	32 (14.6)	271 (15.8)
Stage of Cancer	111	117 (27.7)	127 (11.8)	46 (21)	290 (16.9)
	IV	110 (26)	53 (4.9)	19 (8.7)	182 (10.6)
Histology	Adenocarcinoma	118 (24)	443 (35.4)	83 (31.9)	644 (32.2)
	Squamous cell	374 (76)	807 (64.6)	177 (68.1)	1358 (67.8)
DEM oprolled			222 (12)		
	No	157 (31.9)	238 (19)	58 (22.3)	453 (22.6)
	Yes	335 (68.1)	1012 (81)	202 (77.7)	1549 (77.4)



## Pap Physician Characteristics

Characteristics		Pap Performed and Result known N (%)	Pap performed but result not known N(%)	All N (%)	
Total		1250 (100)	260 (100)	1510 (100)	
		1250 (100)	200 (100)	1310 (100)	
Pap provider's gender	Female	611 (48.9)	74 (28.5)	685 (45.4)	
	Male	583 (46.6)	142 (54.6)	725 (48)	
	Unknown	56 (4.5)	44 (16.9)	100 (6.6)	
Pap provider's specialty	Family practice	808 (64.6)	43 (16.5)	851 (56.4)	
	Gynaecology /OB	357 (28.6)	102 (39.2)	459 (30.4)	
	Nurse	27 (2.2)	(0)	27 (1.8)	
	Other	2 (0.2)	115 (44.2)	117 (7.7)	
	Unknown	56 (4.5)	(0)	56 (3.7)	
Pap provider's location	Rural	76 (6.1)	6 (2.3)	82 (5.4)	
	Urban	1112 (89.1)	210 (80.8)	1322 (87.7)	
	Unknown	62 (5)	44 (16.9)	106 (7)	



## Cytology results by stage of cervical

cytology	IA	IB	Ш	III	IV	missing
AGC/AIS	71 (16.1)	63 (21.28)	18 (11.46)	11 (8.66)	3 (5.66)	28 (15.91)
HSIL/ASC-H	283 (64.17)	145 (48.99)	80 (50.96)	59 (46.46)	15 (28.3)	75 (42.61)
LSIL/ASCUS	45 (10.2)	19 (6.42)	8 (5.1)	13 (10.24)	4 (7.55)	14 (7.95)
Normal	18 (4.08)	40 (13.51)	23 (14.65)	23 (18.11)	22 (41.51)	37 (21.02)
Other Squamous/	8 (1.81)	8 (2.7)	10 (6.37)	8 (6.3)	3 (5.66)	3 (1.7)
Adenocarcinoma	16 (3.63)	21 (7.09)	18 (11.46)	13 (10.24)	6 (11.32)	19 (10.8)
Total	441 (100)	296 (100)	157 (100)	127 (100)	53 (100)	176 (100)



# The median time (months) between the pap test and diagnosis of cervical cancer stratified by FP/OB

The median time (months) from the pap test to diagnosis of cervical cancer stratified by pap test and physician type

	AGC/AIS Median (IQR)	HSIL/ASC-H Median (IQR)	LSIL/ASCUS Median (IQR)	Normal Median (IQR)
Family physician	3 (2 - 4.5)	3 (2 – 5)	4 (2 – 7)	9 (4 - 15)
Gynaecology /OB	2 ( 0 – 3)	2 (1 – 5.5)	3 (2 – 7)	6 (1 – 13)
P - Value	0.001	0.001	0.214	0.018

The median time (months) from the pap test to diagnosis of cervical cancer stratified by stage and physician type STAGE IA STAGE IB STAGE II STAGE III STAGE IV Family physician 4 (2-6) 3 (2-5) 1(1-3.5)3 (1-6) 4 (1-13) Gynaecology /OB 4 (2-7) 1 (0-4) 0.5 (0-2) 1 (0-2) 0 (0-7) P - Value 0.005 0.483 < 0.001 < 0.001 < 0.001

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# The median time (months) from the pap test to diagnosis of cervical cancer

The median time (months) from the pap test to diagnosis of cervical cancer stratified by cytology and physician type, cytology and cancer type stage

	Cytology	IA Median (IQR)	IB Median (IQR)	اا Median (IQR)	III Median (IQR)	IV Median (IQR)
	AGC/AIS	3 (2-6)	3 (2-4)	1 (0.5-1.5)	2 (1-2)	8 (0-16)
Family	HSIL/ASC-H	4 (2-6)	3 (2-5)	2 (1-3)	3 (2-4)	1.5 (1-3)
physician	LSIL/ASCUS	4.5 (2-7)	6 (4-9)	1 (1-10.5)	3 (1-5)	8.5 (0-17)
	Normal	13.5 (5-18)	9 (3-15)	6 (1-16)	9 (5.5-12.5)	13 (7-16)
	AGC/AIS	3 (2-3)	1 (1-3)	0.5 (0-1.5)	0 (0-0)	n/a
Gynaecology /OB	HSIL/ASC-H	4 (2-6.5)	3 (1-7)	1 (0-2)	1 (0-2.5)	1 (0-2)
	LSIL/ASCUS	4 (3-8)	0.5 (0-3)	5 (3-7)	0 (0-8)	7 (1-13)
	Normal	8 (3-14)	2 (1-2)	1 (0-11)	12.5 (8-17)	10 (9-10)



## Model 1: Estimates predicting odds of having a normal or low grade Pap

Univariate			Multivariate				
Characteristics	OR	95% CI	P value	Characteristics	OR	95% CI	P value
Age				Age			
<70	1			<70	1		
>=70	1.6	(1.0 - 2.7)	0.1	>=70	1.3	(0.7 - 2.4)	0.4
Stage				Stage			
IB	1			IB	1		
IA	0.7	0.4 - 1.0		IA	0.7	0.5 - 1.0	
П	1.0	0.6 - 1.7		П	1.1	0.7 - 1.8	
Ш	1.7	1.0 - 2.7	-0.01	Ш	1.9	1.1 - 3.0	
IV	4.2	2.2 - 7.9	<0.01	IV	4.5	2.4 - 8.0	<0.01
Histology				Histology			
squamous	1			squamous	1		
Adenocarcinoma	1.6	(1.2 - 1.6)	<0.01	Adenocarcinoma	1.5	(1.1 - 2.1)	<0.01



## Model 2: Estimates of odds for receiving a colposcopy

l	Jnivariate			Μ	ultivariate		
Characteristics	OR	95% CI	P value	Characteristics	OR	95% CI	P value
Specialty				Specialty			
Gynecology/ OB	1			Gynecology/ OB	1		
Family Physician	2.6	(2.0 - 3.3)	<0.01	Family Physician	2.7	(1.9 - 3.9)	< 0.01
Stage				Stage			
IB	1			IB	1		
IA	3.6	(2.3 - 5.6)		IA	3.0	(1.7 - 4.3)	
II	0.5	(0.4 - 0.8)		П	0.6	(0.4 - 1.0)	
111	0.4	(0.3 - 0.7)			0.4	(0.3 - 0.7)	
IV	0.2	(0.1 - 0.3)	<0.01	IV	0.2	(0.1 - 0.5)	<0.01
Age	0.2	· · · ·		Age	012	, , , , , , , , , , , , , , , , , , ,	
<70	1			<70	1		
70+	0.2	(0.1 - 0.3)	<0.01	70+	0.4	(0.2 - 0.8)	<0.01
Index pap results				Index pap results			
LSIL/ASCUS	1			LSIL/ASCUS	1		
High grade vs LSIL/ASCUS	1.6	(1.1 - 2.8)		High grade	1.6	(1.0 - 3.0)	
Carcinoma vs LSIL/ASCUS	0.2	(0.1 - 0.4)		Carcinoma	0.3	(0.1 - 0.6)	
Normal vs LSIL/ASCUS	0.1	(0.1 - 0.2)	<0.01	Normal	0.2	(0.1 - 0.3)	<0.01



## **Discussion & Recommendations**

- Pap smears are being performed on 60% of patients 0-2 years prior to the confirmation of invasive disease
- 70% of pap smear performed in the setting of invasive disease showed high grade changes, 20% low grade or normal changes and only 7% showed actual cancer cells on pap result
- Cervical cytology results performed 0-2 years prior to diagnosis of invasive disease appear to influence next steps by physicians
- Time to diagnosis of cervical cancer is affected by cytology result 0-2 years prior to diagnosis
- Time to diagnosis may be affected by physician specialty (this is a multifactorial issue which can include training and ability to recognize cervical cancer, pursuit of other investigations such as imaging for symptomatic patients, and access to biopsy which requires referral to gynecologist or colposcopy clinics)
- Improved education required about purpose of pap smear
- Improved education required on signs, symptoms and clinical findings of cervical cancer to avoid diagnostic delays