The British Columbia Randomized Controlled Trial of Cervical Cancer Screening

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British Columbia Cancer Agency

Public Health and Cancer Screening: Promises and Perils, Montreal, 2006

Plan of Talk

1. History and Current Status of Cervical Cancer Screening in British Columbia
2. Potential Impact of HPV Primary Screening Screening in BC
3. BC Randomized Trial

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CARE & RESEARCH

Cette présentation a été effectuée le 27 octobre 2006, au cours du Symposium "La santé publique et le dépistage du cancer : espoirs et réalités" dans le cadre des Journées annuelles de santé publique (JASP) 2006. L'ensemble des présentations est disponible sur le site Web des JASP, à l'adresse http://www.inspq.qc.ca/jasp.

History and Current Status of Cervical Cancer Screening in British Columbia

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Highlights

- British Columbia had the first Pap smear screening program in the world
- Screening started in ~ 1949
- The Program was organized through a single provincial laboratory at the BC Cancer Agency
- Standardized Laboratory Reporting with recommendations for management
- A centrally funded colposcopy program was added in 1975 with affiliated colposcopists

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Highlights

- Laboratory Interprets ~ 600,000 pap smears and Colposcopy Service performs ~ 20,000 procedures per year in 2006
- Program includes physician based follow-up and reminder services, *but **not** patient reminders or invitations*
- Integrated data base created in 1976 of all smears and colposcopies
- Population Cancer Registry created in 1970 and is linked to pap smear database

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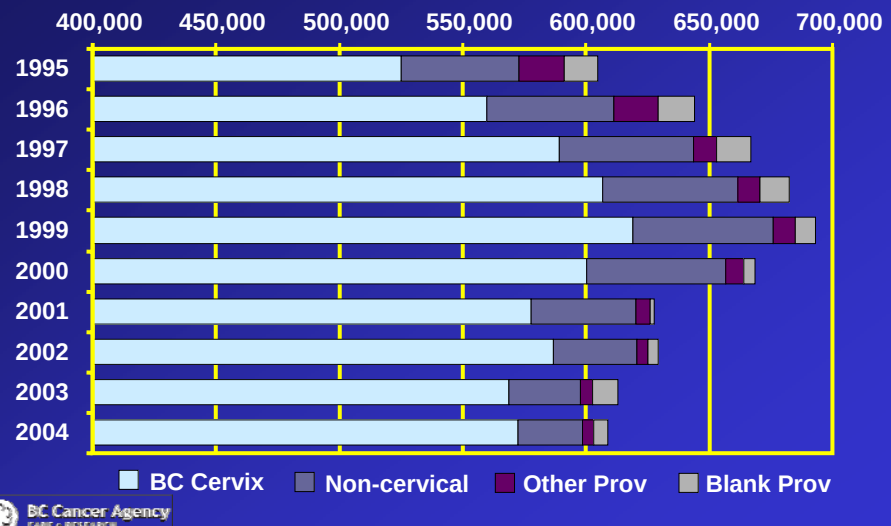
No. of Pap Smears Read at CCSP Laboratory By Calendar Year Smear Was Taken



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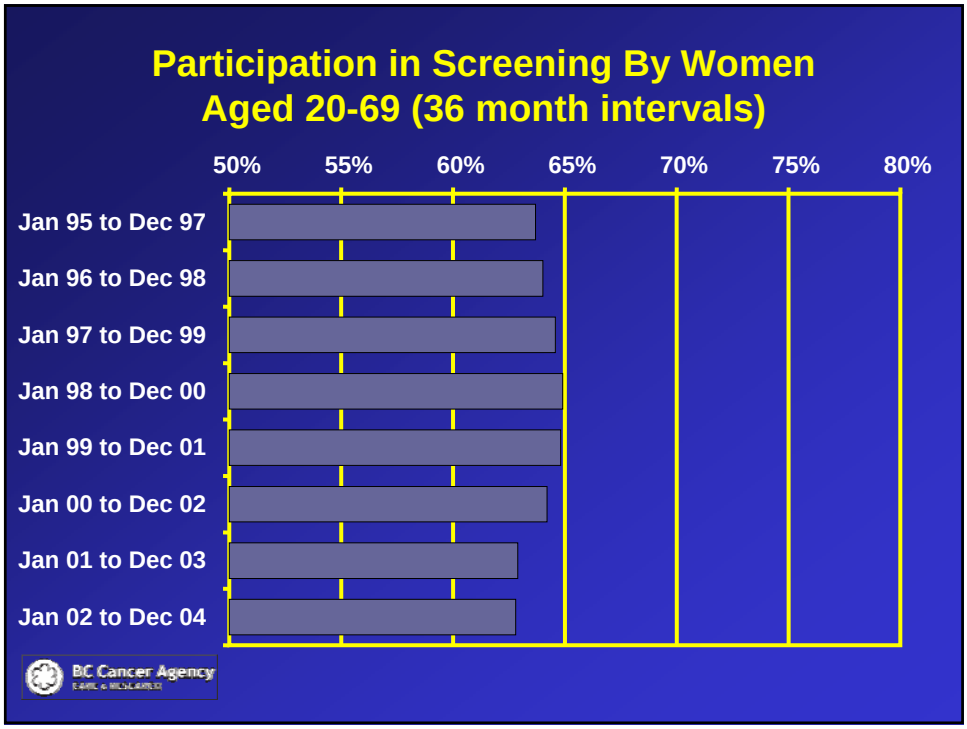
Participation in Screening By Women
Aged 20-69 (36 month intervals)
50%
55%
60%
65%
70%
75%
80%
Jan 95 to Dec 97
Jan 96 to Dec 98
Jan 97 to Dec 99
Jan 98 to Dec 00
Jan 99 to Dec 01
Jan 00 to Dec 02
Jan 01 to Dec 03
Jan 02 to Dec 04
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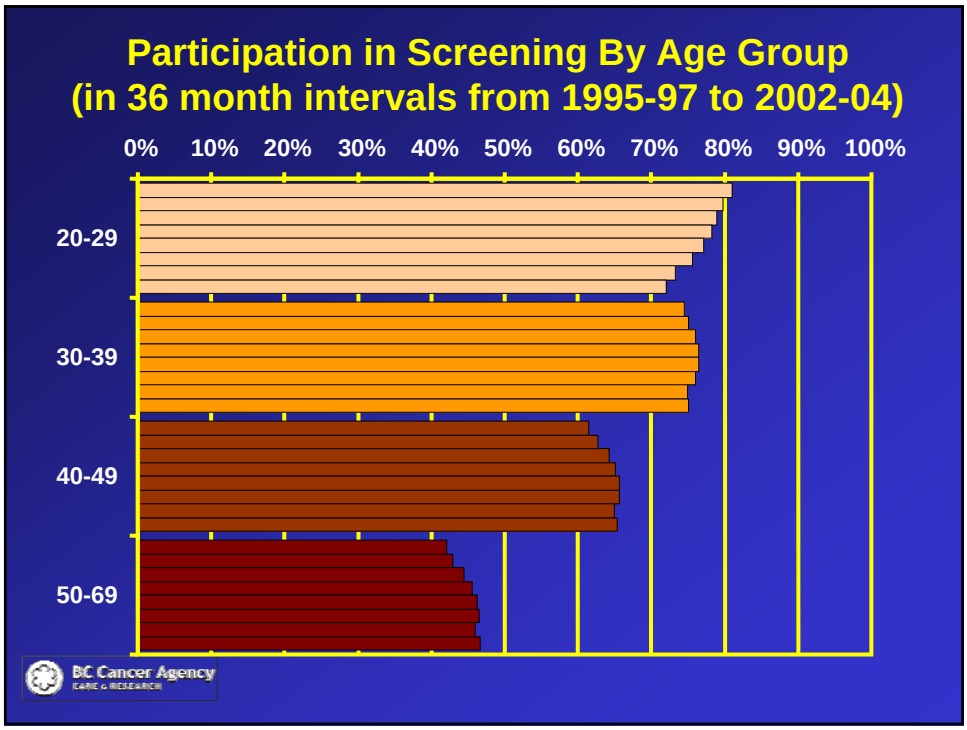
Participation in Screening By Age Group
(in 36 month intervals from 1995-97 to 2002-04)
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
20-29
30-39
40-49
50-69
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Age Distribution of Cases and Deaths from Cervical Cancer in BC in 2003

	20 – 39	40 – 59	60 – 79	80 +	Total
Cases	41	70	29	11	151
Deaths	4	27	12	9	52

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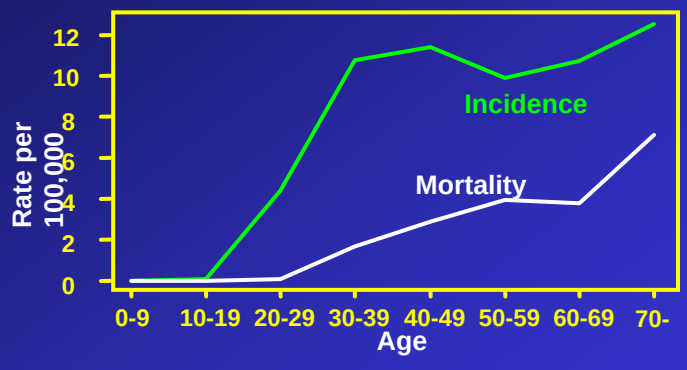
Age-specific Incidence and Mortality rates of Cervical Cancer in BC (1999-2003)



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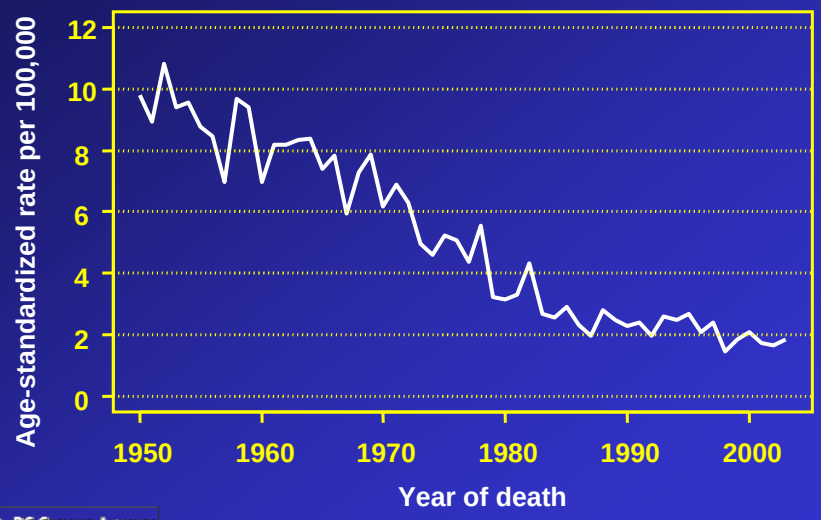
BC Cervical Cancer Mortality: 1950-2003



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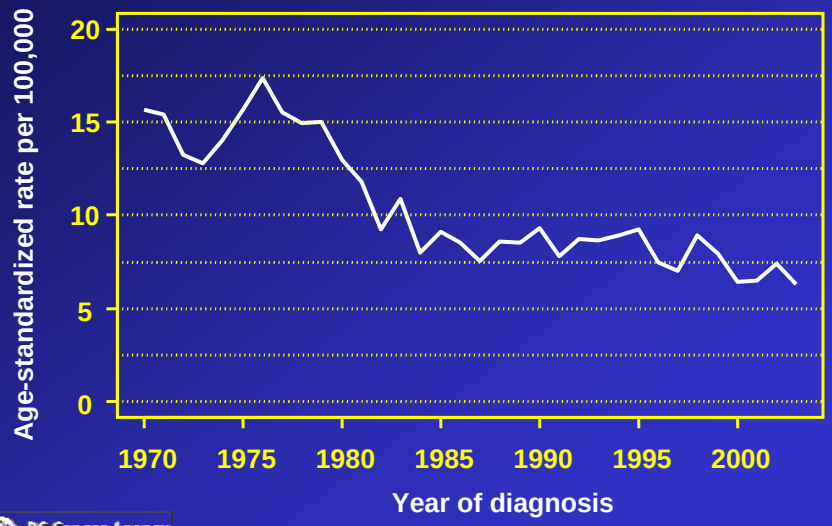
BC Cervical Cancer Incidence: 1970-2003



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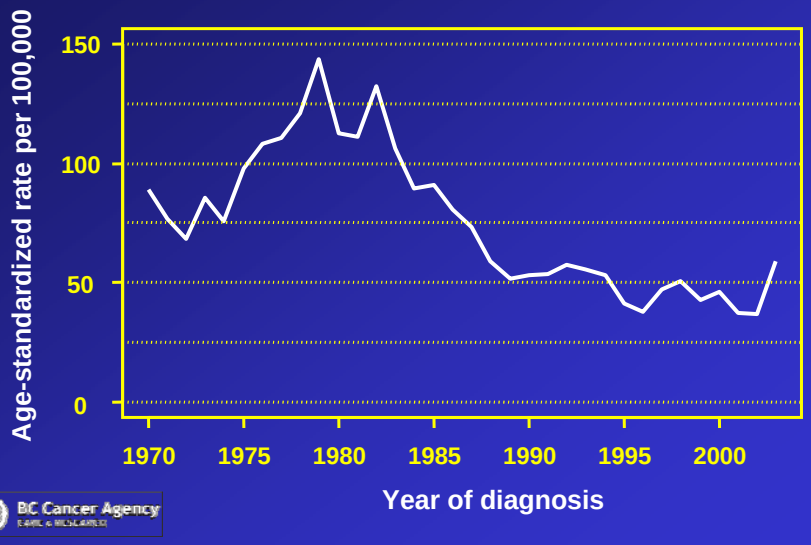
BC In Situ Cervical Cancer Incidence: 1970-2003



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Death from Cervical Cancer and Other Cancers in BC women in 1950 and 2003

	1950	2003
Cervical Cancer	37	52
Other Cancers	688	3,835
Total	725	3,887

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New Cases of Cervical and Other Cancer in BC Women in 1970 and 2003

(source: BC Cancer Registry)

	1970	2003
Cervical Cancers	145	151
Other Cancers	2,642	8,219
Total	2,787	8,370

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So what are the problems!

Cytology is not easy:

- It requires a good quality specimen
- It involves subjective interpretation
- It has defied successful automation and involves repetitive tiring work by technologists
- Public confidence is easily eroded by the high frequency of (multiple) interpretative misses (>5%)
- Sensitivity limited to squamous lesions

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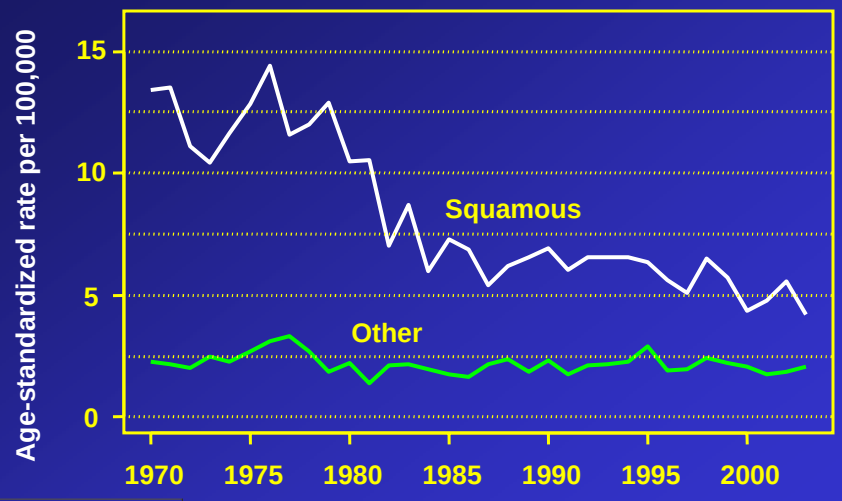
BC Cervical Cancer Incidence by Histology: 1970-2003



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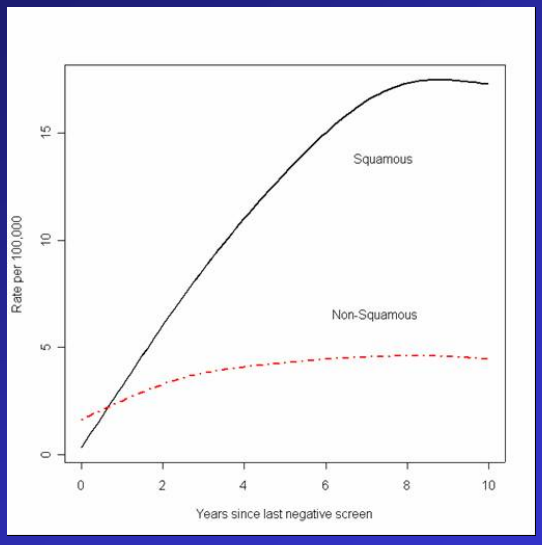
Incidence rates of cancer, squamous and non-squamous, by time since negative screen.



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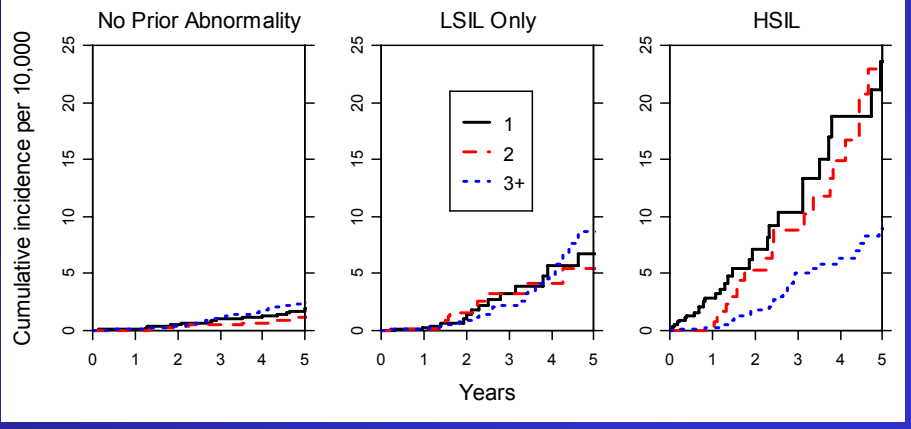
Cumulative Risk of Developing Invasive Squamous Cervical Cancer since last negative screen by NPCNS (number of preceding consecutive negative screens, in patient groups with A) no history of cytologic abnormality, B) history of LSIL only and C) history of HSIL.



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Estimates of Effect of Screening Women Aged 20 – 64 (Source: BMJ, 1986)

Screening Regimen	% Reduction in Cervical Cancer Incidence	Lifetime Number of Screening Pap Smears	Marginal # of Extra Screens per cancer avoided
Every 5 years	84	9	680
Every 3 years	91	15	4,800
Every year	93	45	17,500

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Effect of Frequency of Pap Smear Screening on Cervical Cancer Incidence – BC Analysis*

*Source: Coldman et al, J Med Screen, 2003

Screening Regimen	Age	# of Extra Screens to prevent 1 Cancer
Every 5 years	20 – 69	2,600
Every 3 years	20 – 69	7,800
Every 2 years	20 – 69	11,500
Every year	20 – 69	37,900

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Potential Impact of HPV Primary Screening Screening in BC

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Improvement is Difficult

The preceding slides indicate that conventional Pap smears are close to their effectiveness limit in users

Thus there are two ways to improve cervical cancer screening effectiveness:

- increase the % of women participating in pap smear screening
- improve the effectiveness of the screening test

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Improving the Effectiveness of the Screening Test

There are basically two options available:

- liquid cytology
- HPV testing (high risk types)

In 2003 a Pan Canadian Forum provided recommendations for improving Cervical Cancer Control…

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Pan Canadian Cervical Cancer Forum

It is recommended that:

- Combined cytology-HPV testing in primary screening of women aged 30-69 should be evaluated within the context of an adequate Canadian organized screening program
- …to optimize screening intervals, screening modalities (including cytologic method, and primary screening tool(s)), and target age ranges.
- …to establish appropriate assessment and management strategies to triage HPV positive women, cost-effectiveness, and the acceptance of screening policies by health service providers and women and permit the assessment of emerging technologies that are indicated by strong evidence.

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Stuart G, et al., J Soc Obstet Gynaecol of Canada 2004

HPV Testing for Primary Screening

- HPV testing is not used for primary screening by any provincial or territorial screening program in Canada (in contrast to the United States)
- HPV testing is publicly funded for triage-to-colposcopy in some provinces and also available privately
- There is interest in HPV testing for primary screening:
  - Pan-Canadian cervical cancer forum recommendations
  - Several trials have been conducted, are underway or have been proposed
    - Newfoundland Multi-centre trial – Ratnam, Franco & Ferenczy Cancer Epi Bio Prev. 2000
    - CCCaST – Quebec/Newfoundland (ongoing)

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British Columbia Response

Interest in conducting a trial inside the British Columbia Cervical Screening Program

Major potential benefits of HPV screening:

- increased sensitivity
- increased screening intervals in HPV negative women

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Newfoundland Multi-Centre Trial

Test	Result	Uncorrected		Corrected	
		Sen	Spec	Sen	Spec
Pap Smear	≥ ASCUS	55.9	61.8	40.2	91.6
	≥ LSIL	38.2	80.5	26.8	96.2
	≥ HSIL	20.6	95.2	14.2	99.1
HPV	Positive	85.3	58.0	68.1	90.6
Both	HPV + &/or				
	≥ ASCUS	97.1	38.5	76.3	85.9
	≥ LSIL	97.1	51.3	76.3	89.3
	≥ HSIL	91.2	56.1	72.0	90.3

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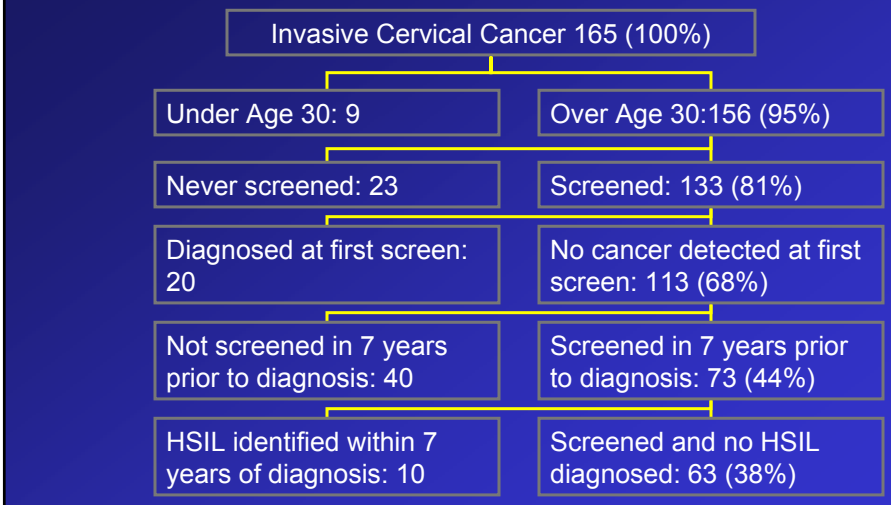
Ratnam, Franco & Ferenczy . Cancer Epi Bio Prev. 2000

Cases Who Could Benefit from Use of HPV for Screening BC Data 2002



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Canadian Cervical Cancer Screening Trial - CCCaST

- Randomised controlled trial to compare the efficacy of the conventional Pap smear and HPV testing for the detection of prevalent and early incident high-grade precancerous lesions and cervical cancers
- To serve as a platform for future studies of cervical cancer etiology and prevention
  - Multi-centre RCT with 2 arms
  - 12,000 women, 30-69 years of age, attending family practice clinics for routine cervical cancer screening in Montreal and Newfoundland
  - 1 year follow-up

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CCCaST

- Advantages:
  - Randomised controlled design
  - Elegant and innovative way to compare HPV only testing to Pap smear only while complying with ethical concerns
  - Balanced design eliminates intervention asymmetry
  - colposcopy of double negatives allows adjustment for verification bias
- Drawbacks:
  - Assesses diagnostic performance for the detection of prevalent and short term incident disease
  - Not set within the context of an organised screening program
  - Does not assess the appropriate safe screening interval

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BC Randomized Trial

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BC Team of Investigators

Investigators:

Philip Davies - *European Cervical Cancer Association*

Andy Coldman, Dirk Van Niekirk, Tom Ehlen, Stuart Peacock - *BC Cancer Agency*

Gina O'Gilvie, Mel Krajden – *BC Centre for Disease Control*

Gavin Stuart, Ruth Elwood-Martin – *University of British Columbia*

Eduardo Franco, *McGill University*

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British Columbia Trial General Objectives

To examine the ability of primary HPV screening to reduce new disease over 4 years of follow-up

To examine the safety of a 4 year screening interval for most women

Use CIN3 as a surrogate outcome for cervical cancer

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British Columbia Trial Specific Objectives

- Evaluate the effectiveness of HPV testing with cytology triage of HPV+
- Evaluate the appropriate screening interval for HPV negative women
- Establish the cost-effectiveness of the screening strategies

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British Columbia Trial

- Design: Randomized 3-arm trial
- Sample size: 11,000 per arm
- Trial Length: Total 7 years
- Primary Outcome variable: CIN3+
- Source of Recruitment: Family practices in greater Vancouver
- Eligibility: Women age 25-69 returning for routine screening, no history of HSIL or CIN

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British Columbia Trial

Three Arms:

- Arm 1: Standard Management Arm – Cytology Screening every 2 years for 2 cycles.
- Arm 2: Experimental Arm – HPV Screening (with cytology triage) every 4 years for 1 cycle.
- Arm 3: Safety Arm – HPV Screening (with cytology triage) every 2 years for 1 cycle.

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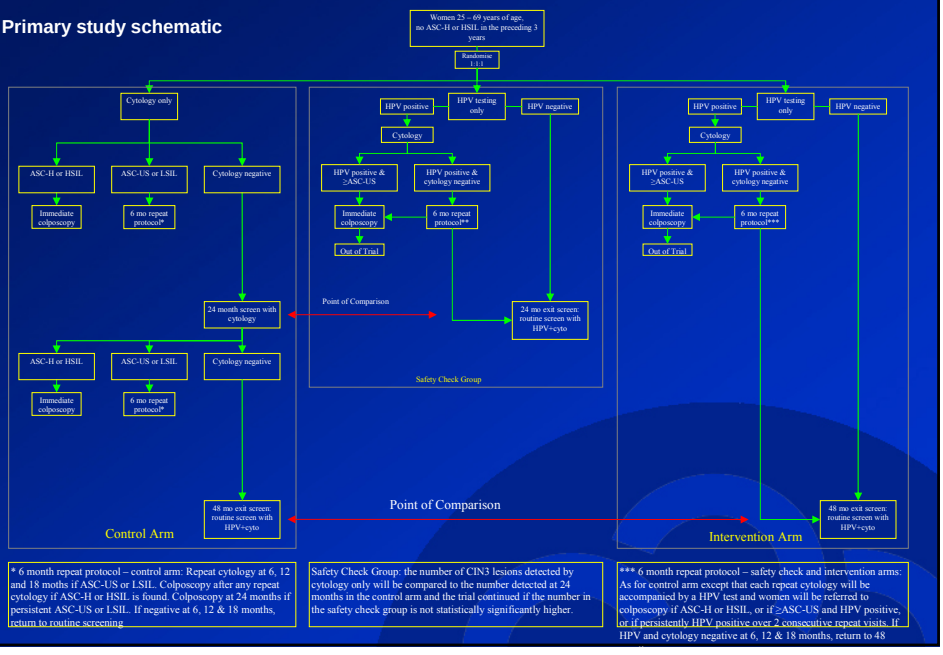
BC HPV Trial

Primary study schematic



* 6 month repeat protocol – control arm: Repeat cytology at 6, 12 and 18 months if ASC-US or LSIL. Colposcopy after any repeat cytology if ASC-H or HSIL is found. Colposcopy at 24 months if persistent ASC-US or LSIL. If negative at 6, 12 & 18 months, return to routine screening.

Safety Check Group: the number of CIN3 lesions detected by cytology only will be compared to the number detected at 24 months in the control arm and the trial continued if the number in the safety check group is not statistically significantly higher.

*** 6 month repeat protocol – safety check and intervention arms: As for control arm except that each repeat cytology will be accompanied by a HPV test and women will be referred to colposcopy if ASC-H or HSIL, or if ≥ASC-US and HPV positive, or if persistently HPV positive over 2 consecutive repeat visits. If HPV and cytology negative at 6, 12 & 18 months, return to 48

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The purpose of the safety arm is to assure that women HPV- have rates of disease sufficiently below those who are cytology – at 2-years to allow extension of the screening interval to 4 years in HPV women

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Arm 1: Standard Management Arm

- Entry Screen: Cytology (Time 0)
  - if + ve: use BC standard practice (ASC-H or HSIL to colpo, ASCUS or LSIL repeat cyto @ 6 months)
- First Repeat Screen: Cytology (24 months)
- Exit Screen: Cytology + HPV (48 months)
  - colpo if HPV+/ASCUS+ or ASC-H/HSIL
  - repeat Screen if HPV+/Cyt -

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Arm 2: Experimental Arm

- Entry Screen: HPV (Time 0)
  - if +ve reflex cytology: ≥ ASCUS to colpo
  - if +ve reflex cytology –ve then repeat @ 6 months
- Exit Screen: Cytology + HPV (48 months)
  - colpo if HPV+/ASCUS+ or ASC-H/HSIL
  - repeat Screen if HPV+/Cyt -

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Arm 3: Safety Arm

- Entry Screen: HPV (Time 0)
  - if +ve reflex cytology: ≥ ASCUS to colpo
  - if +ve reflex cytology –ve then repeat @ 6 months
- Exit Screen: Cytology + HPV (24 months)
  - colpo if HPV+/ASCUS+ or ASC-H/HSIL
  - repeat Screen if HPV+/Cyt -

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Basic Comparisons

Safety: Cumulative CIN3+ post entry at 24 months - Arm3 < 0.8 x Arm1

Effect: Cumulative CIN3+post entry at 48 months - Arm2 v Arm 1

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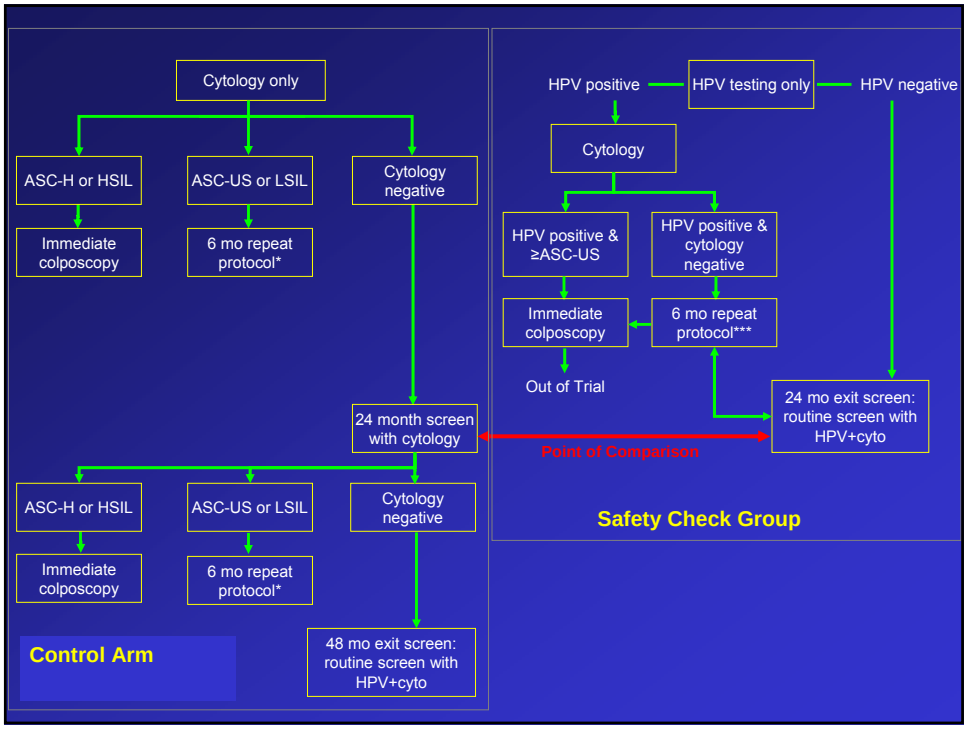

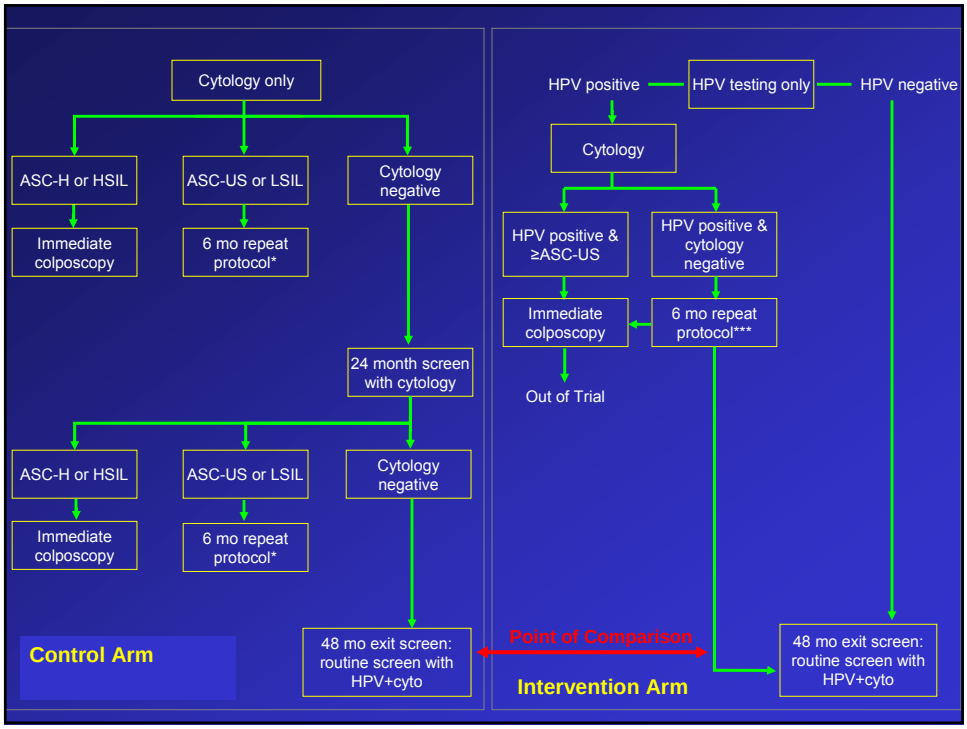

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Safety Comparison will be supervised by a safety monitoring committee composed of external scientists (Chair: AB Miller)

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British Columbia Trial

Current Status:

- CIHR funding secured for 7 years.
- Trial Staff being hired
- Participating Family Physician meeting planned for new year
- Organisation Structures being established

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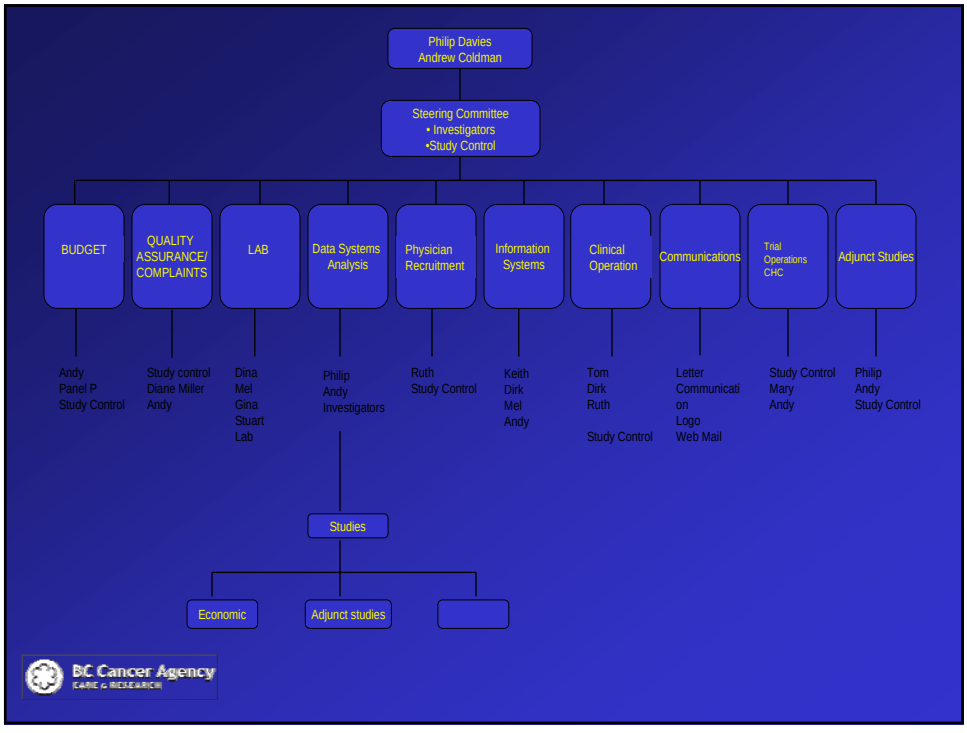

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Please Wish us Luck.

Merci

Thank you.