

Using Population Risks to Guide the Implementation of New Algorithms for Cervical Cancer Prevention

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American Society for Clinical Pathology (ASCP)
November, 2011



Definition of Risk

the possibility that something unpleasant or unwelcome will happen.

Definition of Stratification

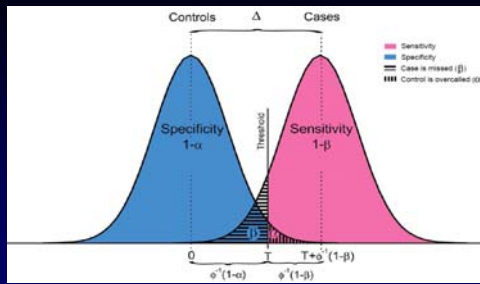
To form, arrange, or deposit in layers

Definition of Risk Stratification

Separating (classifying) people into layers (strata) with different possibilities that something unpleasant or unwelcome will happen.

Today's Talk

- What makes a good biomarker for Risk Stratification?
- Cervix: The model system
- History is important!



Wacholder and Wentzensen, in preparation

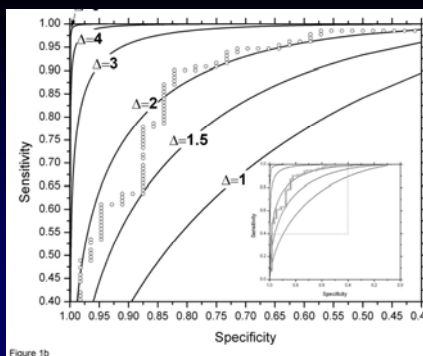
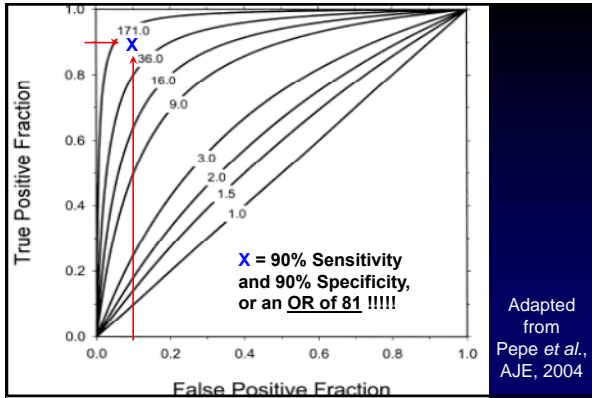
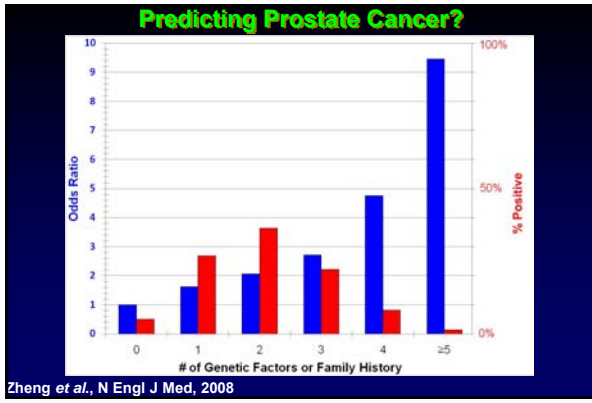
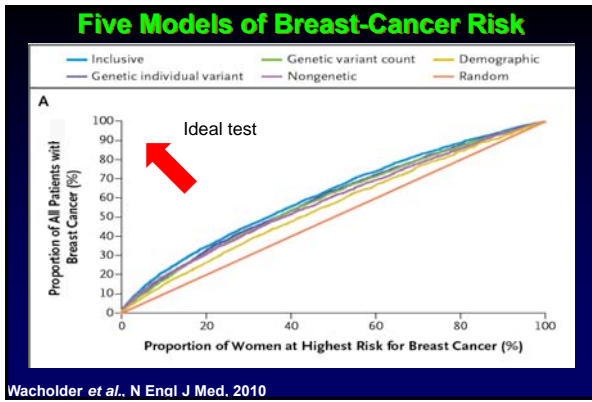


Figure 1b

Wacholder and Wentzensen, in preparation







Risk Stratification for 4 Models

DISTRIBUTION OF ESTIMATED 5-YEAR RISK OF BREAST CANCER
FOR 65-YEAR OLD WHITE AMERICAN WOMEN, ACCORDING TO 4 MODELS

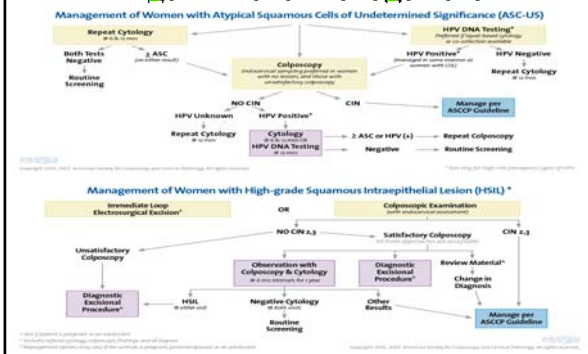
Percentile	MODEL			
	Age alone	Age + Gail factors	Age + Genes	Age + Genes + Gail factors
1%	1.4%	1.0%	0.8%	0.7%
5%	1.4%	1.1%	1.0%	0.9%
25%	1.4%	1.2%	1.2%	1.1%
50%	1.4%	1.3%	1.4%	1.3%
75%	1.4%	1.5%	1.5%	1.6%
95%	1.4%	1.8%	1.8%	1.9%
99%	1.4%	2.1%	1.9%	2.2%
Average Risk	1.4%	1.4%	1.4%	1.4%

Wacholder *et al.*, N Engl J Med, 2010

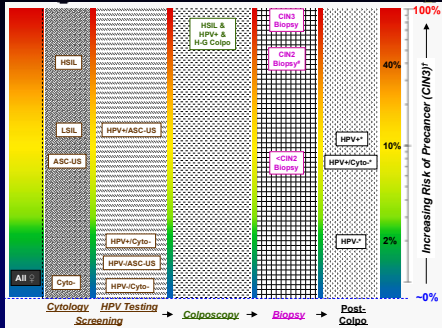
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Algorithms for Management

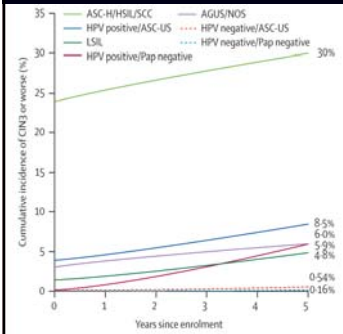


Moving Towards Risk-Based Management

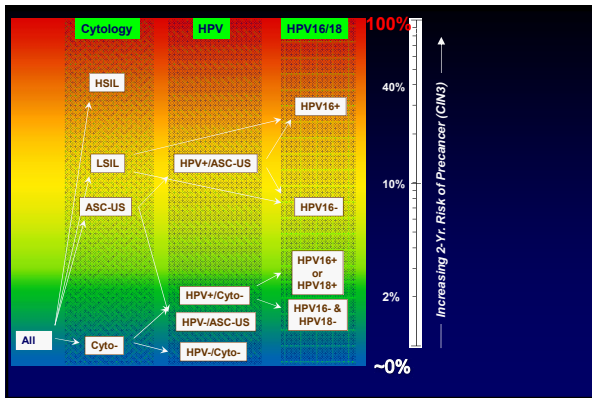


Castle et al., *JLGT*, 2008

Risk Stratification in "Action"



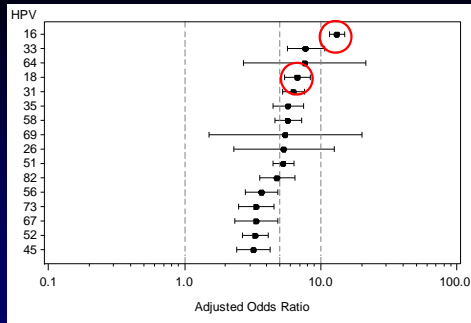
Katki et al., *Lancet Oncol*, 2011



Today's Talk

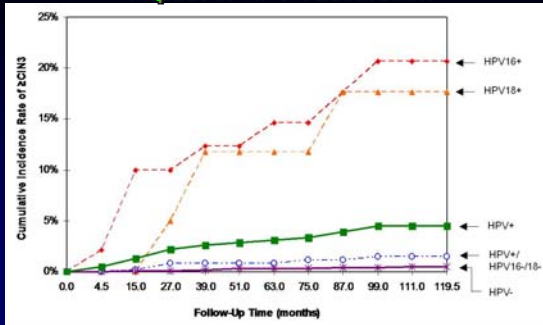
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HPV Genotypes and High-Grade Paps

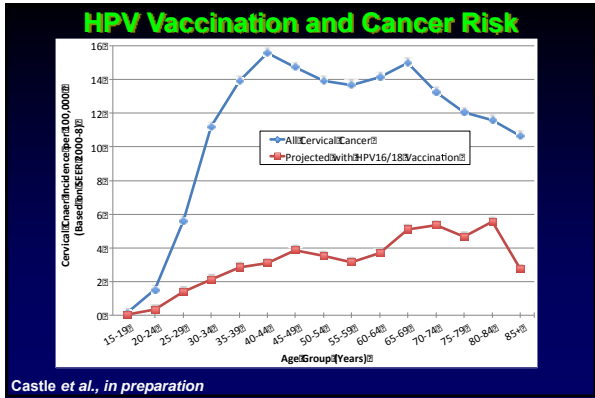


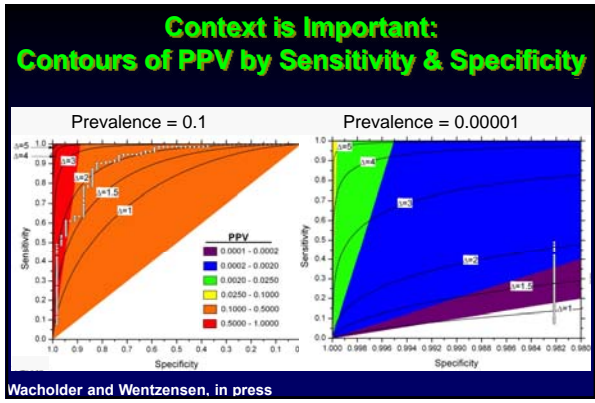
Wheeler et al., in preparation

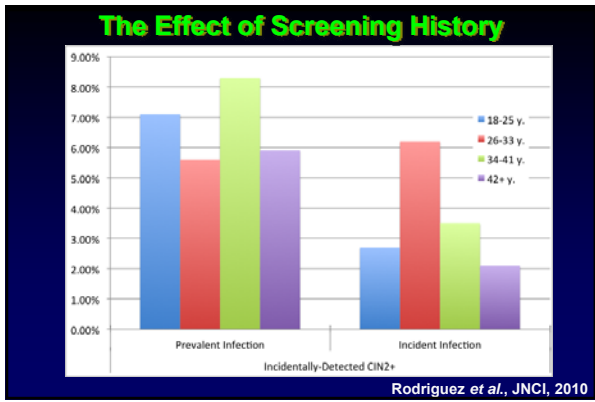
Impact of HPV Vaccination



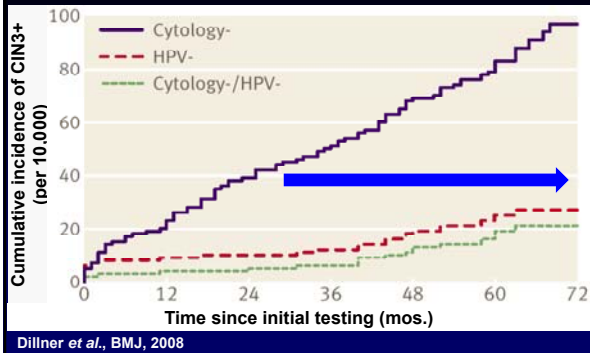
Khan et al., JNCI, 2005



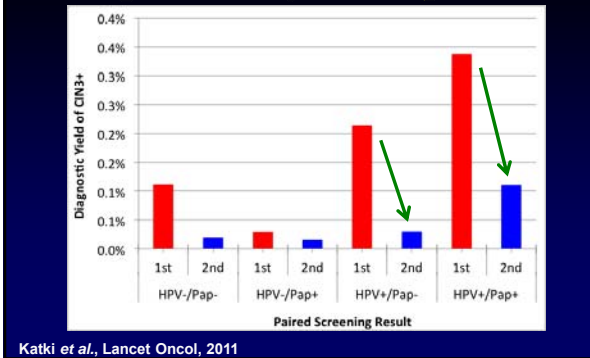




CIN3+ Risk Following a Negative Test



Screening Intervals: Impact on Diagnostic Yields



Variable Risk

Clinically Important:

- HPV Status: New Infection vs. Old (persistent) Infection
- Among HPV+
 - Cytologic Status
 - Biomarker Status: Genotype, mRNA, p16
 - Screening History
 - Vaccine History: Age @ vaccination
 - Age: SCC peaks in the mid-40's (~25-30 years after Sexual Debut)
 - HIV

Not Clinically Important:

- Genetics
- Age of Sexual Debut
- Smoking, Parity, and OC Use

My Guidelines for Risk-Based Approach

1. A marker of risk is only clinically relevant if it has sufficient discriminatory power and penetrance. Weak (virtually all SNPs) and uncommon (e.g., BRCA) markers have no clinical utility to the general populace.
2. It is only useful to stratify the population according to risk if the management differs for the different risk strata.
 1. Not all disease can be prevented. There is a level of irreducible risk.
 2. Excessive measures to reduce low risk to no risk may cause more harm than benefit.

My Guidelines (continued)

5. A risk "score" or probability conveys both dangers of no intervention and intervention.
6. Patients/People at the same risk should be managed similarly, independent of how the risk was assessed.
7. For Cervix, PPV for CIN3+, NPV for Cancer
