WP5 Cancer screening webinar

Risk-stratified screening for cancer

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The screening programmes so far

➔ Screening tests in breast, colorectal and cervical cancer are aimed to find a sign/synptom potentially correlated with the presence of cancer/precursor

➔Same test and same protocol for all target population

➔Age is not a discriminatory factor (everyone will reach the age of the start of the screening programme)

Risk-stratified screening

- The target population is divided into groups with different level of risk of developing a cancer within a certain time

- Different protocols of screening (from the most intense to nothing) are scheduled according to the specific risk of each groups

- The specific risk is predicted by characteristics of the group (for example density of the breast , HPV status , vaccination status, smoking habits, genetic markers …) in se not directly correlated to the presence of the cancer

➔ it is always a population based approach

Two examples of risk stratified screening programme

➔Low dose CT lung cancer screening.

- Screening is reserved only to high risk subjects (heavy smokers)

➔Cervical screening based on HPV testing

- The aim of screening is to identify women with high risk HPV infection (i.e. at higher risk of developing a cervical cancer)

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2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors

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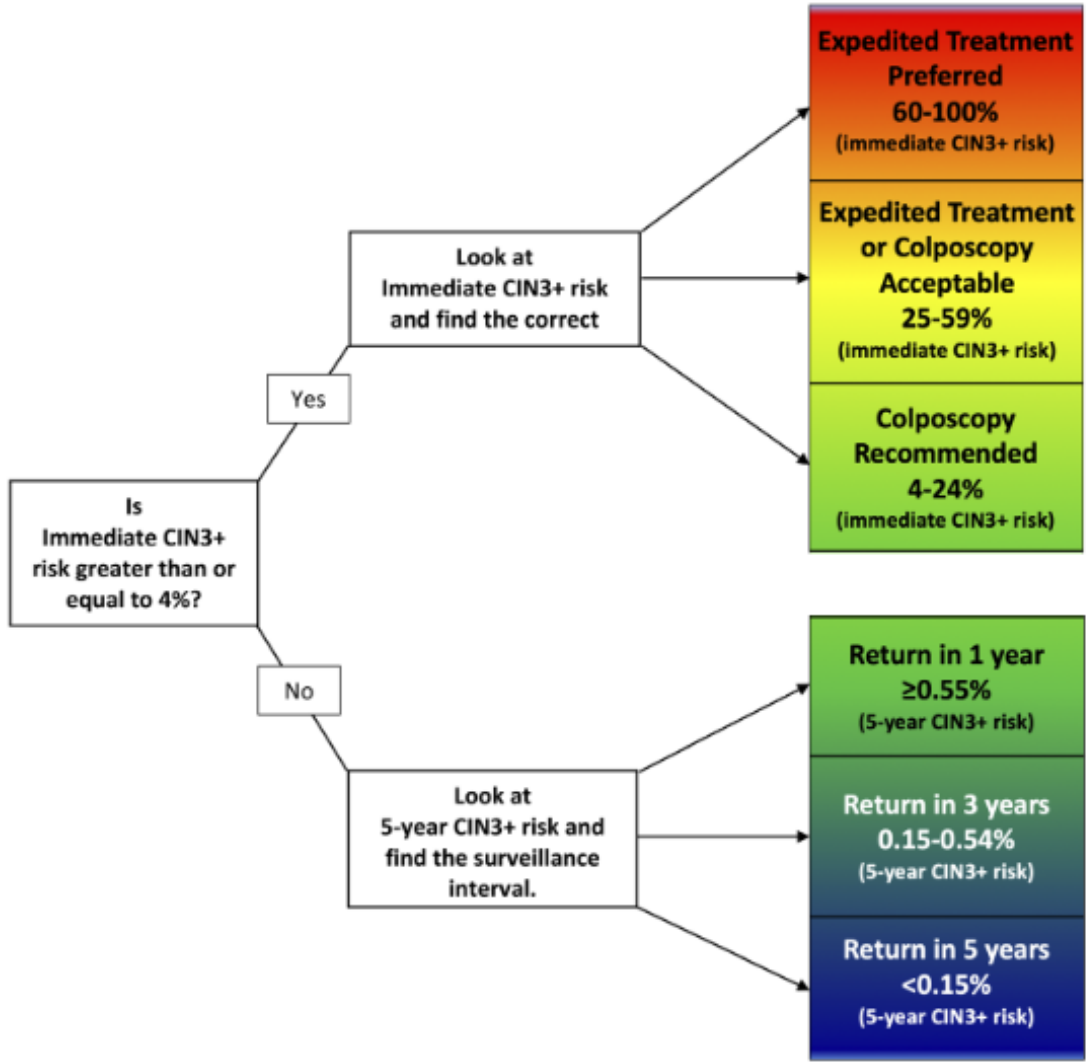
(*J Low Genit Tract Dis* 2020;24: 102–131)

1) Recommendations are based on risk, not results.
2) Recommendations of colposcopy, treatment, or surveillance will be based on a patient's risk of CIN 3+ determined by a combination of current results and past history (including unknown history). The same current test results may yield different management recommendations depending on the history of recent past test results



FIGUR'E 1. This figure demonstrates how patient risk is evaluated. For a given current results and history combination, the immediate CIN 3+ risk is examined. If this risk is 4% or greater, immediate management via colposcopy or treatment is indicated. If the immediate risk is less than 4%, the 5-year CIN 3+ risk is examined to determine whether patients should return in 1, 3, or 5 years.

In which situations a shift from a the generalized screening to risk-adjusted screening could be proposed?

1) There are factors influencing the accuracy of primary test (in particular sensitivity)

2) There are factors influencing the risk of developing a cancer

Density of the breast decreases the sensitivity of mammographic screening and at the same time incresases the risk of developing a breast cancer

Puliti D, Zappa M, Giorgi Rossi P, et al Volumetric breast density and risk of advanced cancers after a negative screening episode: a cohort study. Breast Cancer Res 2018

The highest density category compared with the other categories;

- Has twofold risk invasive BC (RR=2.0 95% CI 1,5-2,8)
- Has fourfold risk for advanced BC (RR=3.8 **95% CI 1.8-80**)

Not simple to find out a solution :

- Different interval of screening ?
- Ultrasound ?
- Tomosyntesis ?

What are the positions in Europe for risk stratification in breast cancer screening?

At the moment for breast cancer screening except for very high risk conditions, age is currently the sole criterion to enter breast cancer screening programs (starting between 40 and 50 to 69-74):

➔ one size fits almost all.

https://ecibc.jrc.ec.europa.eu/

https://ecibc.jrc.ec.europa.eu/recommendations/list/Professional

The ECIBC's Guidelines Development Group (GDG) suggests in very dense breast : (2020)

- **screening with either digital breast tomosynthesis (DBT) or digital mammography**
(conditional recommendation, very low certainty of the evidence)

- **not implementing tailored screening with both DBT and digital mammography**
(conditional recommendation, very low certainty of the evidence)

- **not implementing tailored screening with magnetic resonance imaging (MRI)**
(conditional recommendation, very low certainty of the evidence)

- **not implementing tailored screening with automated breast ultrasound system (ABUS)**
- (conditional recommendation, very low certainty of the evidence)

- **not implementing tailored screening with hand-held ultrasound (HHUS)**
(conditional recommendation, low certainty of the evidence)

Should **tailored** screening with digital breast **tomosynthesis** based on **high** mammographic breast **density**, …, vs. mammography alone… ?

How substantial are the desirable anticipated effects?

Don't know

Research Evidence

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard screening regimen	Risk difference with*
Breast cancer detection rate	8814 (3 observational studies) [a]	⊕⊕OO LOW	**OR 1.76** (1.38 to 2.24) [b c]	Study population	
				635 per 100.000 [a]	**477 more per 100.000** (239 more to 777 more)
False positive recall	3762 (2 observational studies)	⊕⊕OO LOW	**OR 1.41** (1.12 to 1.77) [b]	Low	
				3.800 per 100.000 [d]	**1.476 more per 100.000** (437 more to 2.735 more)
				High	
				9.600 per 100.000 [e]	**3.423 more per 100.000** (1.030 more to 6.222 more)

How substantial are the undesirable anticipated effects?

Varies

a. Median or mean of the control group of the included studies as appropriate unless otherwise specified.
b. Relative effect was adjusted for paired design.
c. Incremental cancer detection rate 540 more per 100.000 (from 200 more to 1020 more)
d. Baseline risk from the control group of Castells 2005 (PMID 16537348).
e. Baseline risk from Hubbard 2011 (PMID 22007042).

The aim of risk-stratified screening is to achieve a better balance between harms and benefit

In presence of a higher prevalence of disease screening tends to be more efficient.

• the Positive Predictive Value (PPV) depends largely on the prevalence of the disease: with higher prevalence we will have a lower proportion of false positive

• On the other hand, risk stratified screening should be also aimed at reducing the intensity of screening in people with lower risk.

•The majority of people attending screening will never have the target cancer but some will suffer some of the undesirable effects of screening.

General remark for risk stratified screening

- As in every screening harms need to be considered co-equally of benefits

- Harms= potential complication of screening test, assessment and treatment, overdiagnosis , anxiety (to be aware of an increased risk is not good per se)

The point of view of the **community**

- The risk-adjusted screening could be a more cost effectiveness
- With the same amount of resources a higher number of saved lives can be obtained, or the same number of saved lives can be obtained with lower amount of resources.

➔ The choice is relatively easy : the evaluation of cost is crucial

The point of view of the individual

If a subjects is stratified in a **Low Risk Group he/she** will experience :

- a lower number of tests;
- a lower lifetime probability of a false positive result;
- lower probability of benign lesion surgical treated
- But also a higher probability of delayed diagnosis of cancer, that could result in more invasive treatments and worst prognosis.
- The **contrary if** the subject is stratified in the **high risk group**

Risk adjusted screening : who decides ?

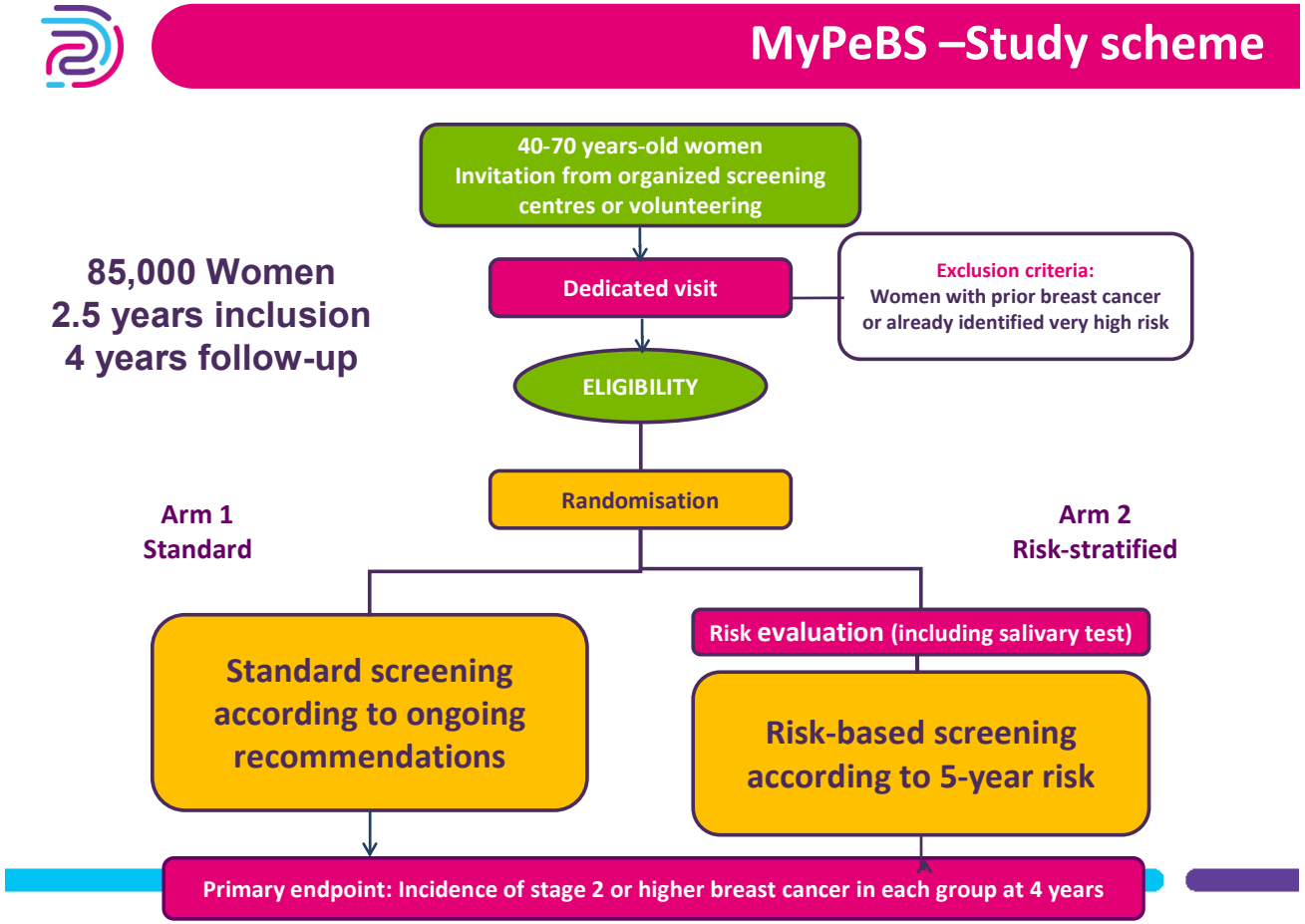
- Who decides the values of the pros and the cons ?

- The community or the subject (via informed consent) ?

On what basis can we decide a risk adjusted screening ?

- A risk based screening can be adopted at a population level only with valid evidence of better risk/benefit ratio.
- In theory RCTs with breast cancer mortality as primary endpoint should be carried out. Practically it is difficult, if not impossible, because large sample size and long period of observation would be needed.
- To adopt early indicators of effectiveness, as rate of advanced cancers, should be considered.

MyPebs –Study



Cervical screening

- In the new cervical cancer screening based on **Papilloma virus (HPV) testing** the test is aimed to identify a situation of higher risk (the infection of high risk HPV virus), making cervical cancer screening actually a risk adjusted protocol, even if HPV test is still considered to be a standard first level test.
- In the next future also **vaccination status** will be considered as a modification factor of screening protocol

Italy - Screening in vaccinated women

The protocol of cervical cancer screening programs will be modified in vaccinated women considering the lower prevalance of HPV 16 and HPV 18 and lower incidence of CIN2+:

-Age to start screening (30+)

-Screening test: HPV instead of Pap

-Interval between test (7-10 yrs vs 5 yrs)

Florence, 5/11/2015

OSSERVATORIO NAZIONALE SCREENING

GISCi

Gruppo Italiano Screening del Cervicocarcinoma

Consensus Conference

per la definizione del percorso di screening del cervicocarcinoma nelle donne vaccinate contro l'HPV

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Cervical cancer screening in women vaccinated against human papillomavirus infection: Recommendations from a consensus conference

Paolo Giorgi Rossi [a,b], Francesca Carozzi [c,*], Antonio Federici [d], Guglielmo Ronco [e], Marco Zappa [f], Silvia Franceschi [g], The Italian Screening in HPV vaccinated girls Consensus Conference group [1]:

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Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline Lise M Helsingen LM et al , : BMJ 2019;

- These recommendations apply to adults aged 50-79 years with no prior screening, no symptoms of colorectal cancer, and a life expectancy of at least 15 years. **For individuals with an estimated 15-year colorectal cancer risk below 3%, we suggest no screening (weak recommendation).** For individuals with an estimated 15-year risk above 3%, we suggest screening with one of the four screening options: FIT every year, FIT every two years, a single sigmoidoscopy, or a single colonoscopy (weak recommendation).

Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline Helsingen LM et al , : BMJ 2019;

- Factors considered : Age Gender BMI smoking habits Family History of CRC etc.
- Advantages : a lower probability of having a CRC or dying from CRC
- Disadvantages: probability of having one or more colonoscopy with rare but serious complications

➔ Who decides the values ?

➔How large is the uncertainty of the estimate ?

Uncertainty (example)

- In the paper Fit every two years produces ”little or no effect on cancer incidence “ (5% of reduction in cancer incidence)
- In Italy (FIT every two years) we carried out some some studies on this topic in different areas and with different approches
- *Ventura et al Dig Liver Dis 2014, (-22% per protocol after 12 years)*
- *Giorgi Rossi P et al Am J Gastro 2015 (- 10% Intention to treat after 8 years)*

➔ The reduction in cancer incidence for people attending CRC Screening is close to 15- 20%

Conclusion

- Risk adjusted screening can enhance the cost effectiveness of screening
- The efficacy and the side effect of alternative protocols should be carefully evaluated by RCT
- The sustainability (cost, resources, organizational aspects) should be deeply evaluated
- The communication and the psychological impact of such an approach should be monitored and evaluated.

Thank you

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