Risk stratified screening programmes

Marco Zappa

Clinical Epidemiology Unit

ISPRO Florence Italy

Paolo Giorgi Rossi

IRCSS Reggio Emilia Italy

The screening so far

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

➔ Same test and same protocol for all target population

Risk-stratified screening

- Different protocols of screening (from the more intensive to nothing) are scheduled in a group of subjects of the target population according to the specific risk of developing a cancer within a certain lag of time

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

➔ it is a population based screening

In which situations a shift from a the generalized screening to risk-stratified 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 groups;

- 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 ?

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 and consequently, the number of persons referred to assessment will be lower,

•On the other hand, risk stratified screening should be also aimed at reducing the intensity of screening in people with lower risk. We must consider that the majority of people participating in screening will never have the target cancer but many will suffer some of the undesirable effects of screening.

The point of view of the **community**

With a risk stratified screening a more cost effectiveness result can be obtained:

➔ 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 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 side effects (ex. lower irradiation) ;

• 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**

➔ **Who decides the value?**

General remarks 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)

On what basis can we decide a risk stratified 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.

General remarks

- 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.

Lung cancer screening

Several risk prediction models have been developed :

LLP, PLCO2012 etc…

•The LLP Lung Cancer Risk Model provides an estimate of the probability that an individual, with a specified combination of risk factors, will develop a lung cancer within a 5-year period.
All risk factors are gathered by questionnaire

•Only subjects with a 2.5% risk over 5 yrs will be included in screening in the NHS England protocol

Covariates used in LLP model

Covariates	B-coefficient (SE)	HR (95%CI)	*P*-value
Age	0.036	1.04 (1.02-1.06)	<0.001
Gender (men vs. women)	0.391	1.48 (1.10-1.98)	0.009
Smoking duration	0.043	1.04 (1.03-1.05)	<0.001
COPD	0.890	2.43 (1.79-3.30)	<0.001
Prior diagnosis of malignant tumour	1.044	2.84(2.08-3.89)	<0.001
Family history of lung cancer			
None	Reference	Reference	
Early onset (<60 years)	0.521	1.68 (1.04-2.72)	0.034
Late onset ((≥60 years)	0.071	1.05(0.72-1.59)	0.722

Abbreviations: COPD= chronic obstructive pulmonary disease; HR= hazard ratio; SE = standard error

Colorectal cancer screening

- Family History
- Genetic markers
- It has been suggested that the cumulative value of Fecal haemoglobin

in the previous negative test is a strong predictor of the risk of detecting advanced adenomas or cancer in the subsequent test

(Auge et al 2014, Buron et al 2018, Senore et al Gut in press)

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

- Factors considered : Age Gender BMI smoking habits Family History of CRC
- Advantages : a lower probability of having a CRC or dying from CRC
- Disadvantages: probability of having one or more colonoscopy

➔ Are these models valid?

➔ Who decides the values ?

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).

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 stratified 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 shall 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 vs Pap
- Interval between test (10 y vs 5 y)

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]:

ISPRO

Breast cancer screening

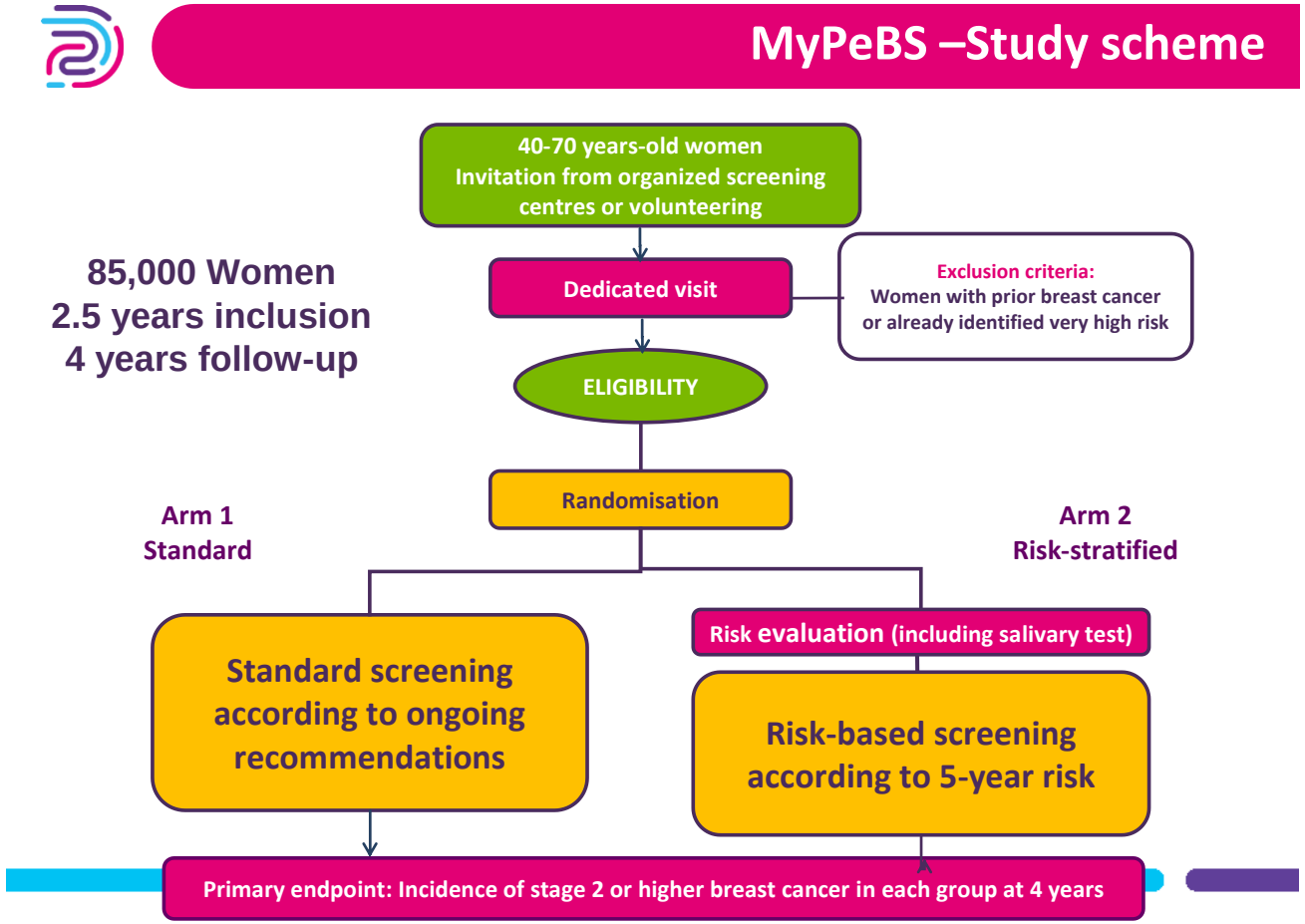
What are the positions in Europe for risk stratification in breast cancer screening?

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/

MyPebs –Study



Thank you