



EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Directorate F - Health, Consumers & Reference Materials (Ispra)
Health in Society

European Commission Initiative on Breast Cancer (ECIBC): European guidelines on breast cancer screening and diagnosis Evidence profile

Healthcare question	Should annual vs. biennial mammography screening be used for early detection of breast cancer in women aged 45 to 49?
Date	September 2016
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Abbreviations	CI: Confidence interval RR: Risk ratio OR: Odds ratio

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Annual mammography screening	Biennial mammography screening	Relative (95% CI)	Absolute (95% CI)		
Breast cancer mortality												
5 1,2,3,4,5,a	randomised trials	not serious	not serious	very serious b,c	serious ^d	none	329/92837 (0.4%)	183/19867 (0.9%)	RR 0.92 (0.63 to 1.35)	74 fewer per 100,000 (from 322 more to 341 fewer)	⊕○○○ VERY LOW	CRITICAL

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Annual mammography screening	Biennial mammography screening	Relative (95% CI)	Absolute (95% CI)		
Breast cancer death averted (modelling studies)												
2 ^{6,7,e}	observational studies	serious ^{f,g}	not serious	very serious ^{h,i,j}	not serious	none			Ratio B/A (range) -- (1.75 to 2.31)	-- per 100,000 (from 30 more to 51 more)	⊕○○○ VERY LOW	CRITICAL
Stage of breast cancer (IIB-IV)												
1 ⁸	observational studies	serious ^k	not serious	very serious ^{c,l}	not serious	none	2052 cases 3573 controls		OR 0.85 (0.75 to 0.96)	-	⊕○○○ VERY LOW	CRITICAL
							-	0.0%		-- per -- (from -- to --)		
QALYs (modelling studies)												
2 ^{6,m}	observational studies	not serious	not serious	very serious ^{h,i,j}	not serious	none			Ratio A/B: - - (1.09 to 1.45)	480 more per 100,000 (from -- to --)	⊕○○○ VERY LOW	CRITICAL
Interval cancer												
1 ^{9,n}	observational studies	serious ^k	serious	very serious ^o	not serious	none	10/14285 (0.1%)	5/3333 (0.2%)	RR 0.46 (-- to --)	80 fewer per 100,000 (from -- to --)	⊕○○○ VERY LOW	CRITICAL
Overdiagnosis (modelling studies)												
2 ^{6,10,m}	observational studies	not serious	not serious	serious ^{h,i,j}	not serious	none			Ratio A/B -- (-- to 1.2)	200 more per 100,000 (from -- to --)	⊕○○○ VERY LOW	CRITICAL
False positive results -10 year cumulative probability ^p												
1 ¹¹	observational studies	serious ^q	not serious	very serious ^{c,l}	not serious	none	Annual screening 67% (95%CI 65% to 68%) Biennial screening 45% (95%CI 44% to 46%) Difference: 22,000 more per 100,000.				⊕○○○ VERY LOW	CRITICAL
False positive biopsy recommendation -10 year cumulative probability ^r												
1 ¹¹	observational studies	serious ^q	not serious	very serious ^{c,l}	not serious	none	Annual screening 11% (10% to 13%) Biennial screening 6% (5% to 7%) Difference: 5,000 more per 100,000.				⊕○○○ VERY LOW	CRITICAL

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Annual mammography screening	Biennial mammography screening	Relative (95% CI)	Absolute (95% CI)		
Radiation induce breast cancer (modelling studies)												
1 ^s	observational studies	serious _{f,g}	not serious	very serious _{h,j,i,t}	not serious	none			Ratio A/B 1.78 (-- to --)	14 more per 100,000 (from -- to --)	⊕○○○ VERY LOW	CRITICAL
Death by radiation induced breast cancer (modelling studies)												
1 ^s	observational studies	serious _{f,g}	not serious	very serious _{h,j,i,t}	not serious	none			Ratio A/B 1.5 (-- to --)	2 more per 100,000 (from -- to --)	⊕○○○ VERY LOW	CRITICAL

Explanations

- Rate ratio comparing annual screening relative to biennial screening was estimated by an indirect meta-analysis. Absolute effects were calculated taken as basal risk the proportion of breast cancer mortality in intervention arms of the trials of annual screening.
- Comparison was done by performing indirect meta-analysis of RCT (n=3) of annual mammography interval versus no screening against RCT of biennial mammography interval versus no screening.
- Estimations based in studies that included women from 40 to 49 years old
- Wide confidence interval based in indirect comparison
- Modelling studies used different number of women screened for calculations: 1,000 in 2 studies, and 100,000 in 2 studies. One modelling study (Vilaprinco 2017) gave inconsistent results in this year period (less deaths averted for annual interval) and then it was not included in the results of breast cancer deaths averted.
- One or more studies did not report information about external validation for the estimated parameters of the models.
- One or more studies did not report sensitivity analysis information for the estimated parameters of the models.
- The comparison for any interval in the models was a no screening scenario. No direct comparisons were reported.
- Modelling studies with data available for the 45 to 49 age period. Results were calculated by subtracting the absolute number of events from overlapping periods of screening i.e. 45 to 74 minus 50 to 74.
- Most models were constructed using data of surveillance registries from United States.
- Intervals were classified in base of the month ranges elapsed between two screening mammograms prior to diagnosis. Potential high risk of misclassification.
- Results were extracted from groups of women with selected characteristics (e.g. normal weight, fatty or scattered fibroglandular breast density, or white race).
- Modelling study, used 1,000 women screened for calculations.

- n. From the In the Swedish two county trial with an average screening interval of 24 months, the calculated interval cancers for >0 to <12 months was 38%, and for 12 to <24 months was 68% (Tabar 1987).
- o. Estimations based in one study that included women from 40 to 79 years old
- p. Two modelling studies estimated the number of false positive result in annual screening of 9,150 to 56,700 and for biennial of 6,301 to 26,700 per 100,000 screened women from 45 to 49 years old (difference 2,849 to 30,000 more events).
- q. No clear information of how the intervals were estimated for the false positive cohorts or the number of individuals per interval.
- r. Two modelling studies estimated the number of benign biopsy results in annual screening of 409 to 5,600 and for biennial of 208 to 3,000 per 100,000 screened women from 45 to 49 years old (difference 201 to 2,600 more events).
- s. Modelling study; used 100,000 women screened for estimates.
- t. Incremental effects were estimated for a screening program starting at 50 and ending at 74.

References

1. Moss, S. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years 'follow-up: a randomised controlled trial. *Lancet Oncol*; 2015.
2. Habbema, J. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of Greater New York Study. 1986.
3. Miller, A. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ*; 2014.
4. Nystrom, L. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet*; 2002.
5. Tabar, L. The Swedish two-county trial twenty years later. *Radiol Clin North Am*; 2000.
6. Mandelblatt, J. Collaborative modeling of the benefits and harms associated with different U.S. breast cancer screening strategies. *Ann Intern Med*; 2016.
7. Miglioretti, J. Radiation-induced breast cancer incidence and mortality from digital mammography screening. *Ann Intern Med*; 2016.
8. Miglioretti, DL. Breast tumor prognostic characteristics and biennial vs annual mammography, age, and menopausal status. *JAMA Oncol*; 2015.
9. Hunt, KA. Outcome analysis for women undergoing annual versus biennial screening mammography: a review of 24,211 examinations. *AJR Am J Roentgenol*; 1999.
10. Vilapriyo, E. Cost-effectiveness and harm-benefit analyses of risk-based screening strategies for breast cancer. *PLoS One*; 2014.
11. Dittus, K. Impact of mammography screening interval on breast cancer diagnosis by menopausal status and BMI. *J Gen Intern Med* ;