Clinical Perspective: Acceptable absolutes and what to do with all the keratinocyte cancers

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Acceptable absolutes

False Negative rates of screening

- Melanomas detected post-screening examination
  - Sensitivity at screening examination
  - Natural history of primary melanoma
    - Growth rates
    - Incidence of Interval tumours

False Negative rates screening Fritschi et al. Am J Epidem. 2006:164:385-390

- Lions Cancer Institute WA dermatologists/plastic surgeons community based 1994-2002
- Post screens follow-up cancer registry 2yrs

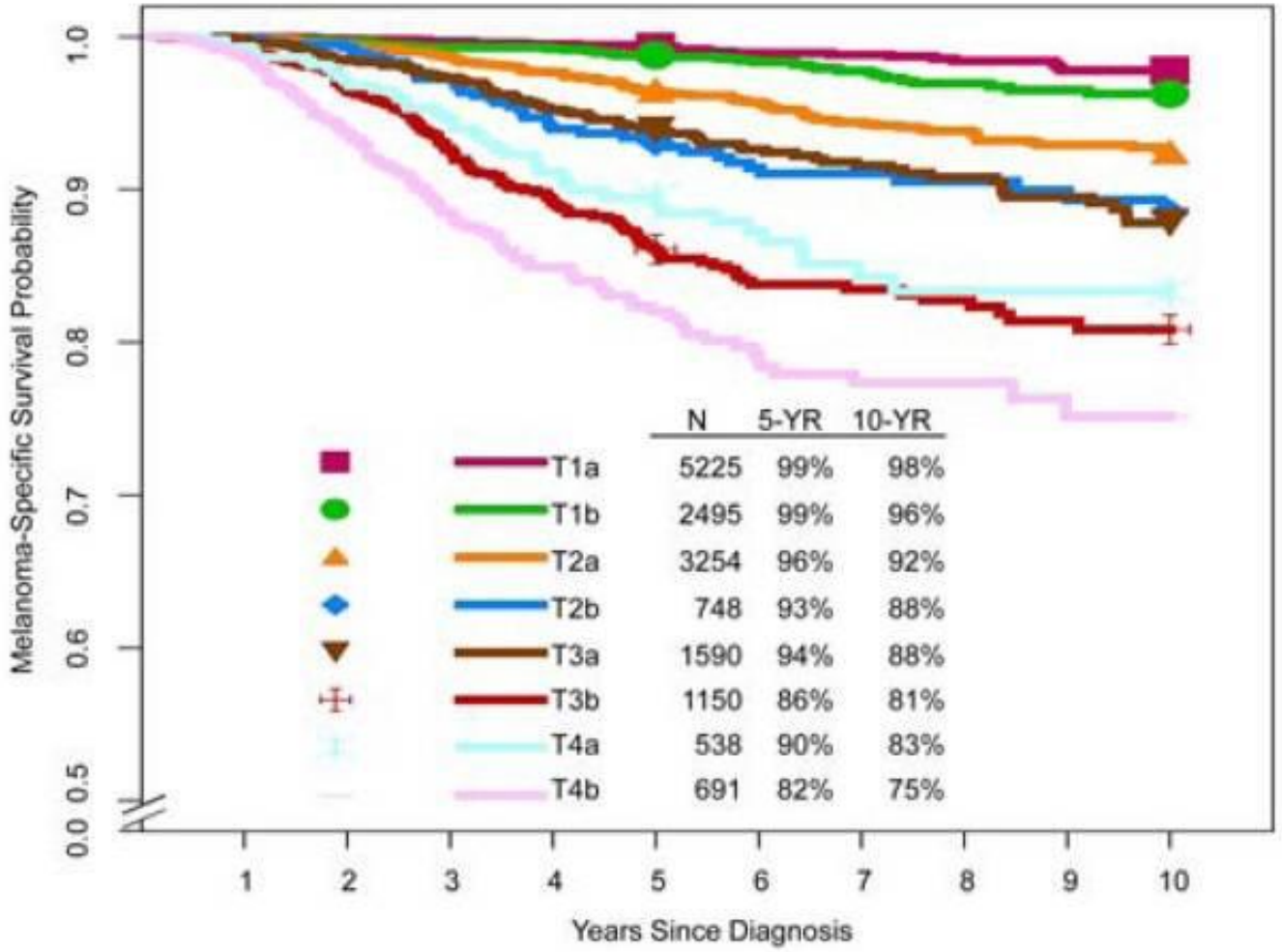
False Negative rates screening Fritschi et al. Am J Epidem. 2006:164:385-390

	Year 1	Year 2
Sensitivity invasive MM % (95% CI)	70 (51-84)	49 (34-64)

False Negative rates screening – What is acceptable?

	Year 1	Year 2
Sensitivity invasive MM % (95% CI)	70 (51-84)	49 (34-64)

If false negative MM thin (T1a) then ?OK



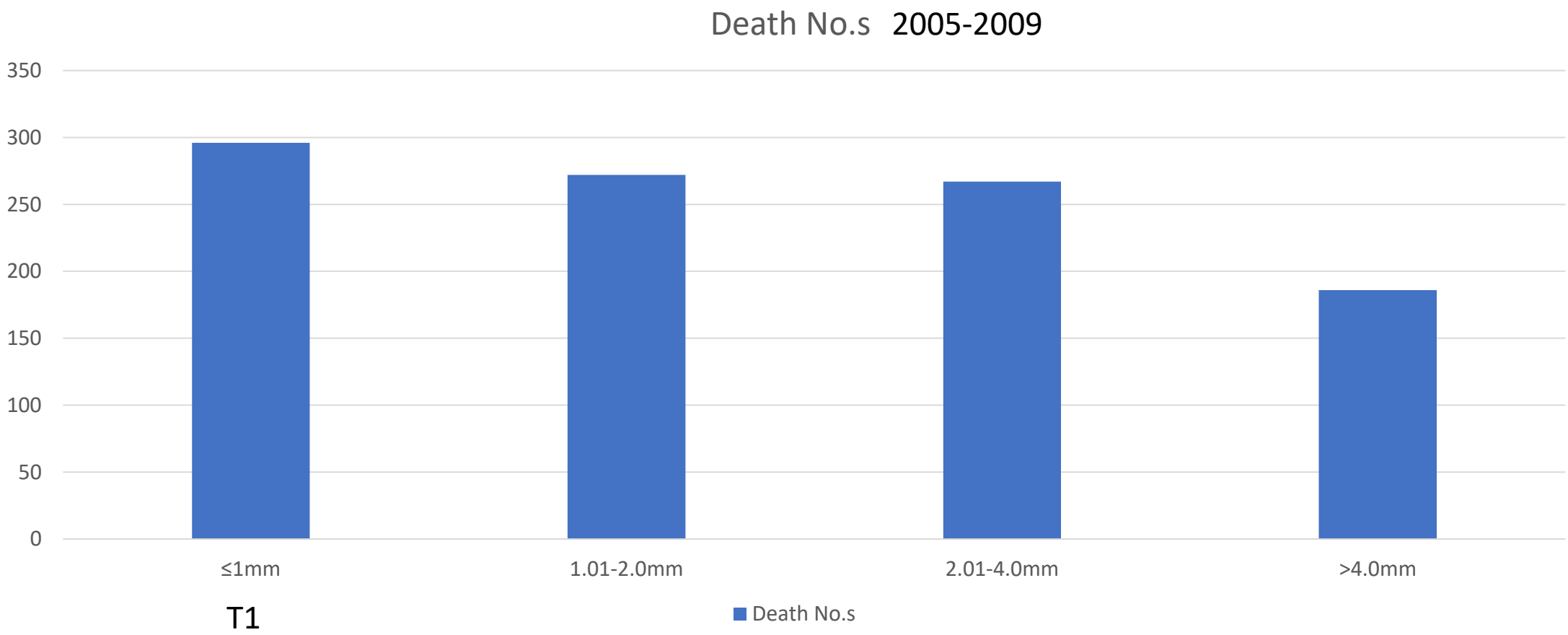
T1a < 0.8mm non-ulcerative

T1b < 1.0mm incl. ulcerative

Gershenwald et al. CA Cancer J Clin 2017;67:472-92

Who dies from Melanoma (QLD)? Whiteman et al.

J Invest Derm 2015;135:1190-



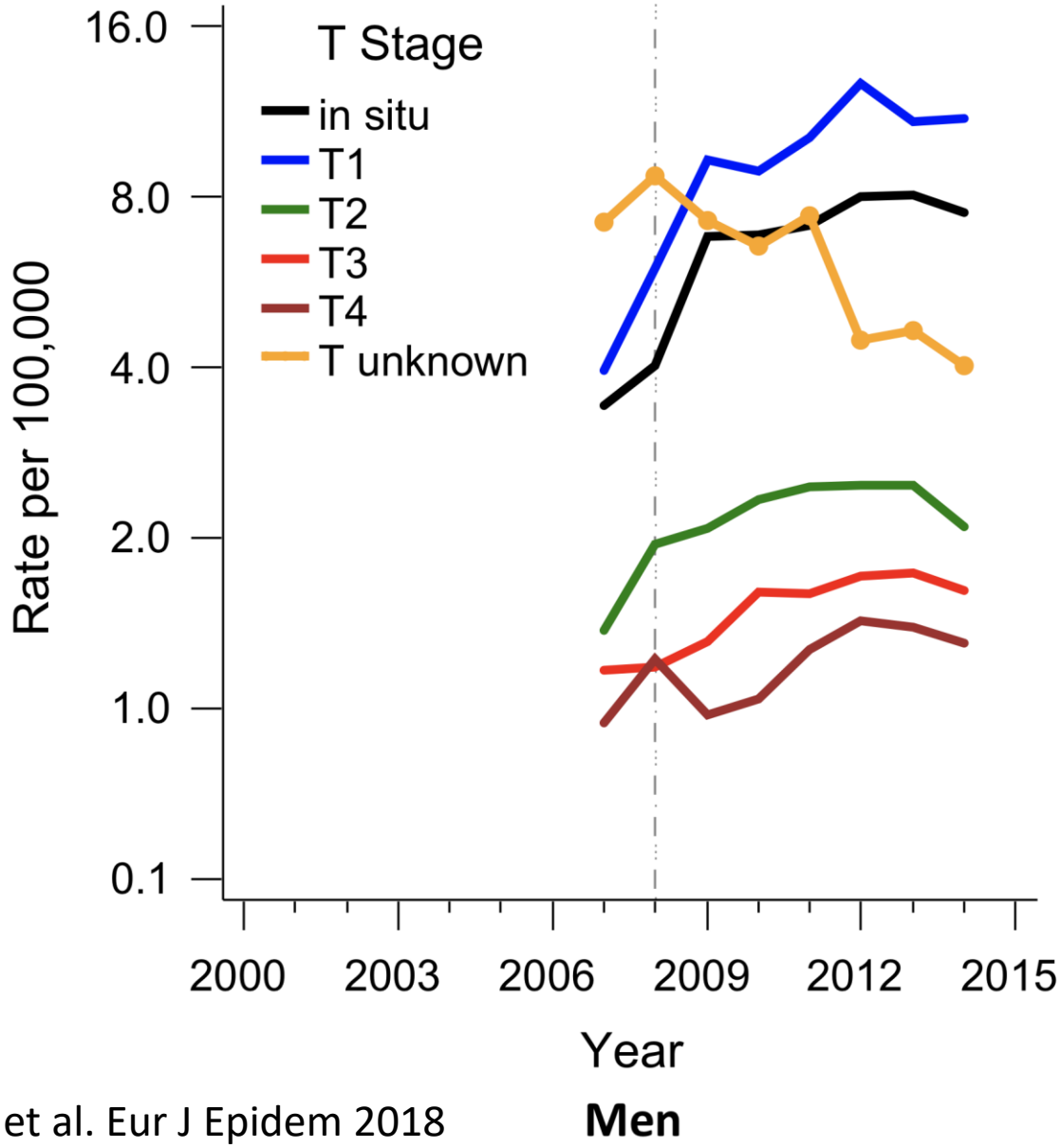
T1

Are we reducing thick tumours?

7yrs after screening began in Germany

Stang et al. Eur J Epidemiology 2018: 33:303-12

- Data from North Rhine Westphalia (pop 18 Million)
- 2008-2015 (longest data yet published)



Stang et al. Eur J Epidem 2018

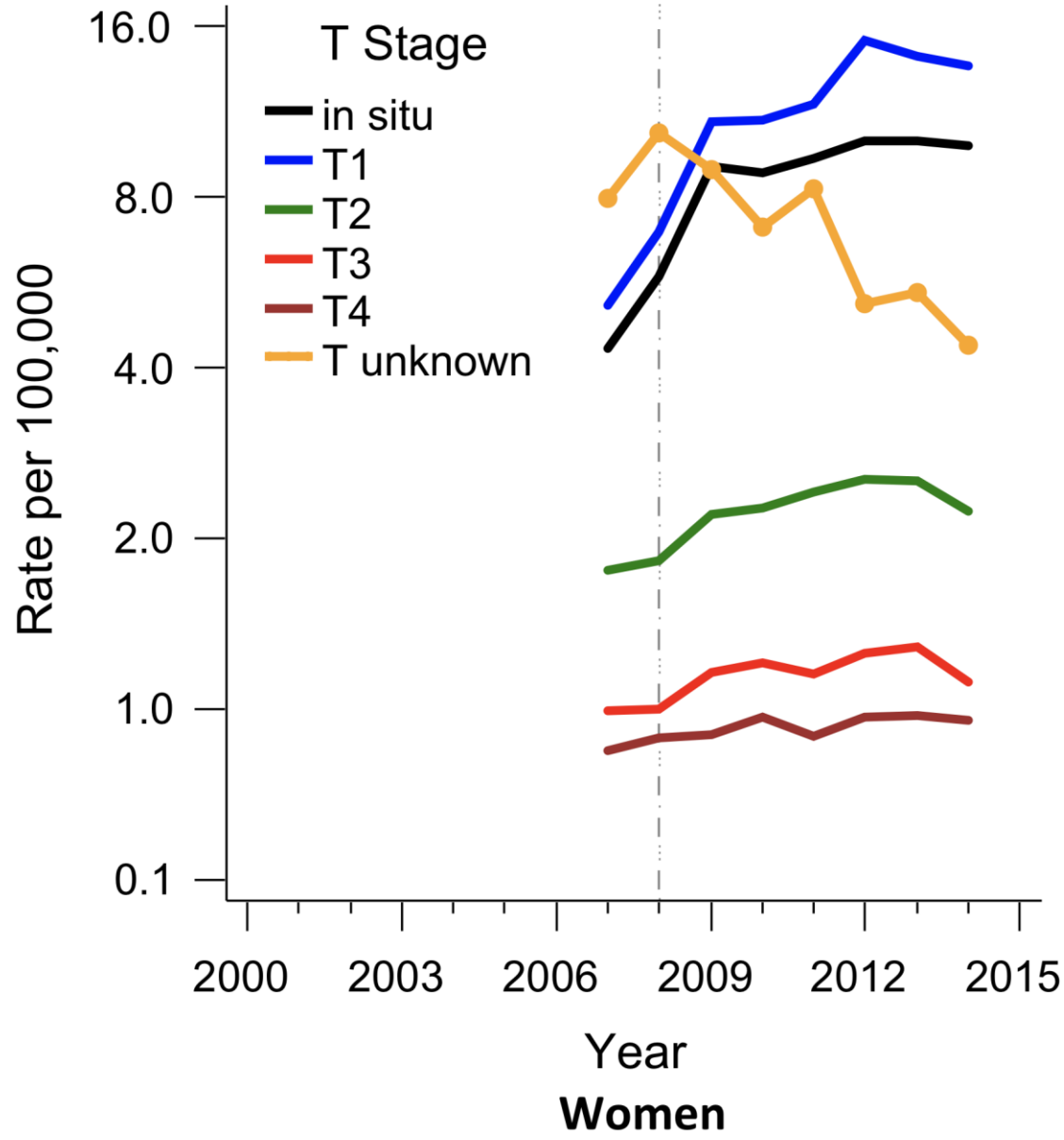
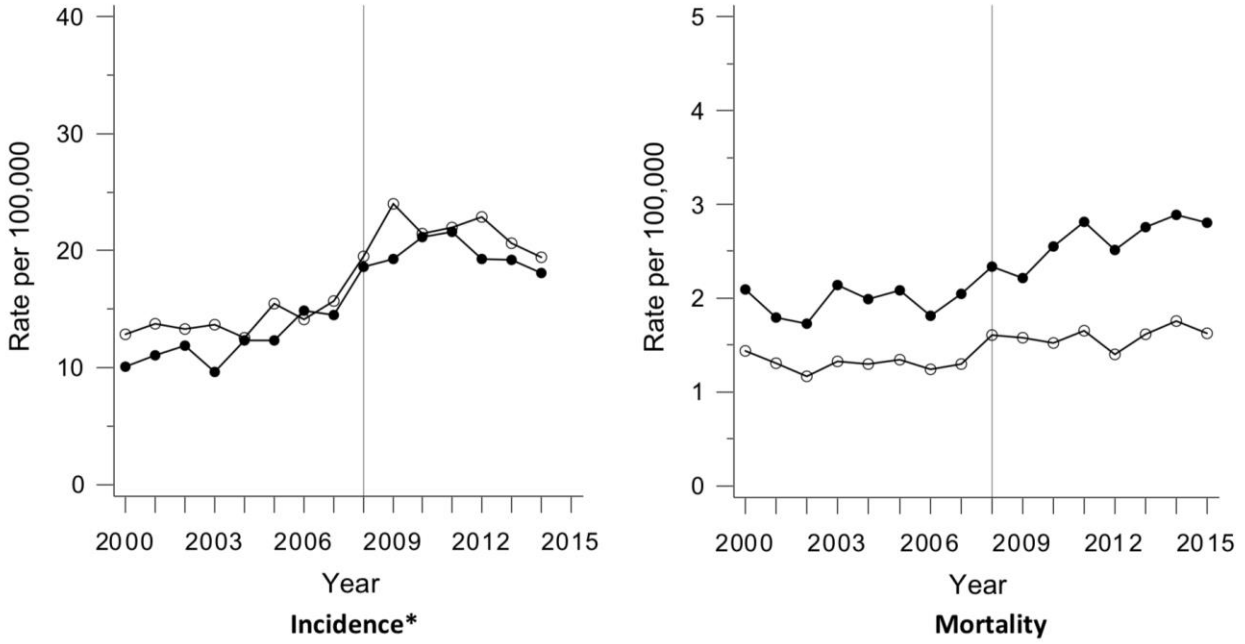
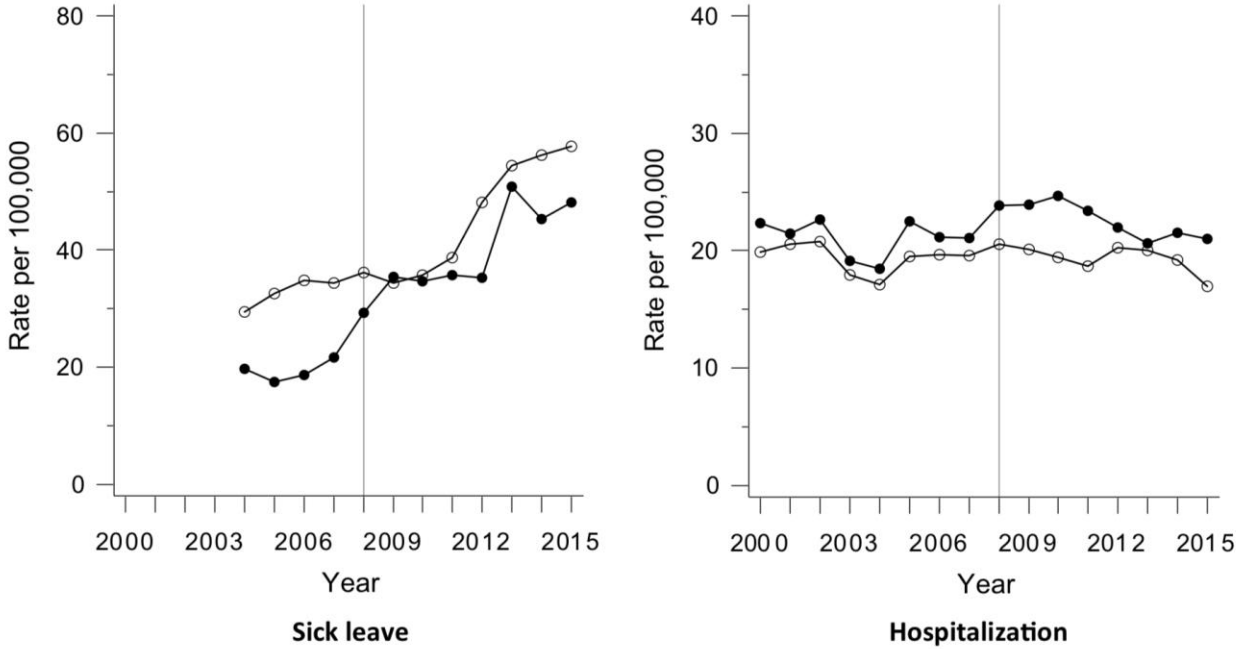


Fig. 3 T-stage specific age-standardized incidence rates of skin melanoma in North Rhine-Westphalia, Germany, 2007–2014.

Melanoma





● Men

Mortality increase mainly elderly men and women (>70, >75 yrs)

University of Pittsburgh prospective screening study Ferris et al. JAMA Oncol. 2017;3:1112-5

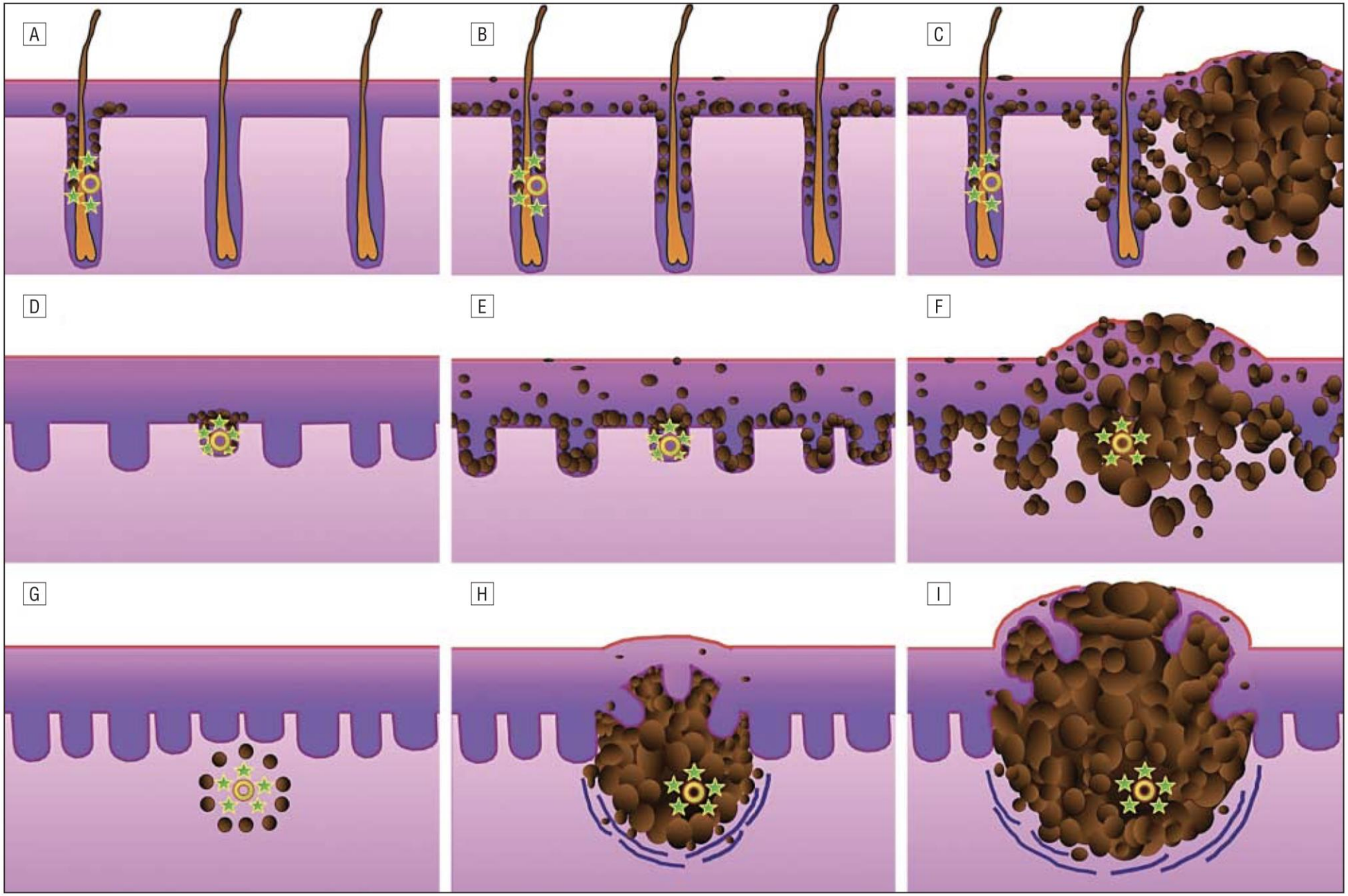
- Eligible $\geq 35\ yrs$ if saw an internet training offered-PCP in 2014
- 53 000 Total body skin examination vs 280 000 not screened
- Adjusted RR 2.4 (95%CI:1.7-3.4) diagnosed melanoma in screened
  - Thinner MM in screened 0.37 vs 0.65mm
  - No difference in thick melanoma $\geq$ 1 mm

Population-based Case-control QLD*

- First invasive primary MM diagnosed 20-75yrs between 2000-2003

- Whole-body skin exam three years before diagnosis 14% lower risk of thick MM (>0.75mm) & risk decreased as thickness increased (40% lower for MM >3mm).

*Aitken J et al. Int J Cancer 2010;126:450-58



Zalaudek et al. Arch Dermatol. 2008;144:1375-

Acceptable absolutes – *Tumour thickness*

- Reduction in absolute no.s of > T1a MM*
  - Inter-screening tumours
  - Total population

*T1a < 0.8mm non-ulcerative

Potential Harms screening*

- False Positive Rates
- Overdiagnosis ➢ overtreatment
- Negative psychosocial consequences
- Somatic complications

* Heleno B et al. BMJ 2013;347:f5334

Potential Harms Skin Cancer screening**

- False Positive Rates
- Overdiagnosis ➢ overtreatment NOT REPORTED
- Negative psychosocial consequences NOT REPORTED
- Somatic complications

**Systematic review US Preventative Services Task Force: Wernli K et al. AHRQ Publication No. 14-05210-EF-1 (2016)

False Positive Rates (NNT*): SCREEN STUDY (Schleswig-Holstein)

- July 2003 – June 2004
- Population-based > 20yrs age
- Whole-body examination by mainly non-dermatologists ➢ referred suspicious lesions/higher risk patients to dermatologists

* Number Needed to Treat

Number of excisions to detect 1 cancer* NNT

Number of Excisions Needed to Detect 1 Case	Melanoma	Squamous Cell Carcinoma	Basal Cell Carcinoma
Overall	28	41	9
Female			
Age, years			
20–34	41	N/A	138
35–49	30	579	34
50–64	24	72	8
≥65	22	14	4
Total	**28**	**56**	**10**
Male			
Age, years			
20–34	52	926	116
35–49	55	435	35
50–64	22	48	7
≥65	20	12	4
Total	**28**	**28**	**7**

Waldmann et al. Arch Dermatol. 2012:148:903-10

*Based on one excision/person & one malignant per tumour per person

What is acceptable Melanoma NNT?

- NNT is not a measure of diagnostic sensitivity
- Impacts on Morbidity and Cost-effectiveness

- GPs Australian (generalist) 17
- GPs (solo skin cancer practice) 8.5
- Dermatologists Australia 12
- Dermatologists USA 15

Rolfe HM. Austral. J Dermatol. 2012;53:112-117

Rosendahl C et al. J Am Acad Dematol. 2012;67:846-52

Wilson R et al. J Dermatol. Treat 2012;23:65-9

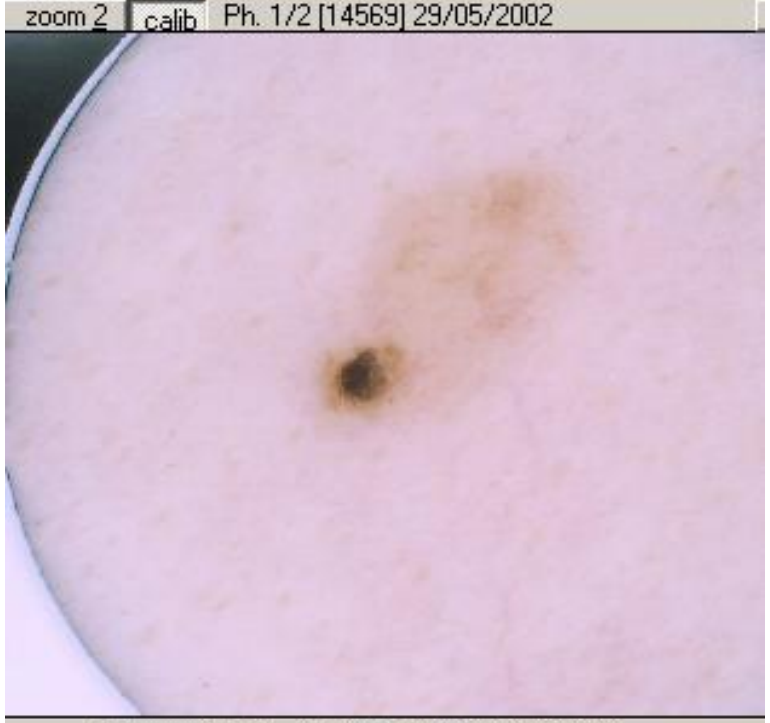
What is acceptable Melanoma NNT?

- Need to use diagnostic techniques that *reduce NNT* while *increasing sensitivity* for MM

http://wiki.cancer.org.au/

Dermoscopy

Sequential digital dermoscopy monitoring



Cost difference – Tromme I et al. PLos One 2014; 14;9:e109339

- Belgium dermatologists (short and long term monitoring)

- Benign:Melanoma ratio excisions
  - 8.1 vs 2.5 (Dermoscopy monitoring)

- €1,600 vs 1,000 (monitoring) per melanoma detected

COST DIFFERENCE: Watts C et al. J Clin Oncol 2017:35:63-71

- AUSTRALIAN HIGH RISK COHORT: Dermoscopy monitoring and total body photography vs Standard Care over 10yrs

- A$6800 per patient SAVED
  - Earlier detection
  - Reduced excisions

Stang et al. Eur J Epidemiology 2018: 33:303-12

- Number needed to screen (NNS) to prevent 1 extra death of melanoma in 2015*

34 000

- 90% deaths occurred people >50yrs of age

NNS 26 000

* Assuming a risk reduction of 50% due to screening

NNS for other cancers to save 1 extra life

- 320 Heavy smokers aged 55-74 yrs lung CT
- 402 aged 55-64 yrs sigmoidoscopy colorectal
- 500-1000 aged 50-69 yrs women biannual mammography for 10yrs

NNS 26 000 >50yrs for Melanoma

Stang et al 2018

NNS for skin cancer to save 1 extra life

- What is acceptable ?

NNS of skin cancer to save 1 extra life

- What is acceptable ?

NNS 26 000 >50yrs for Melanoma*

Similar figure calculated for Australia**

*Stang et al 2018

** Gilmour S, Plos One 2017

NNS of skin cancer to save 1 extra life

- What is acceptable ?

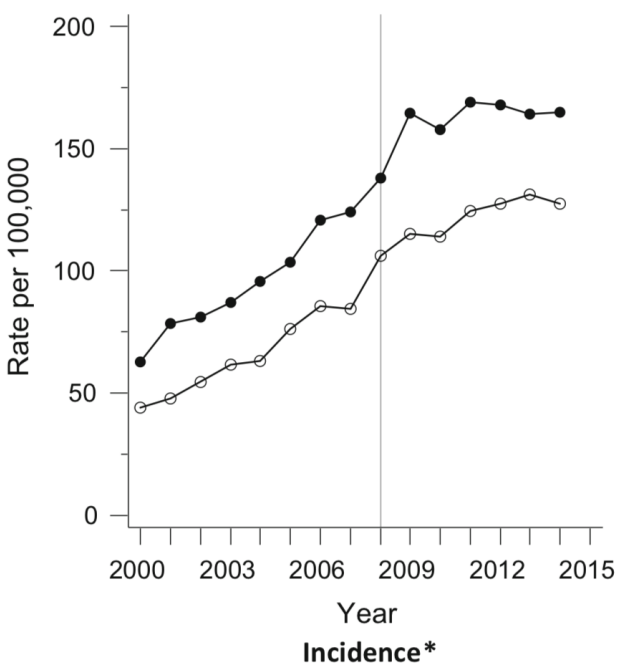
Reduce by targeting high risk individuals

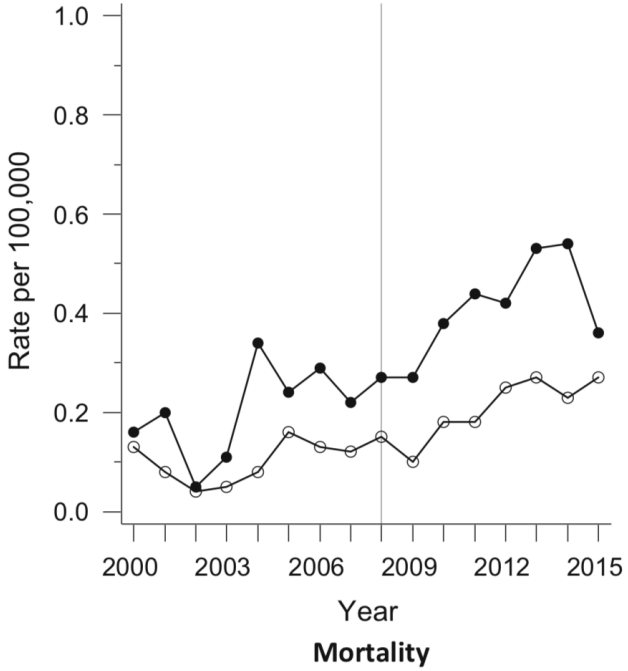
What are we going to do with all the keratinocyte cancers?

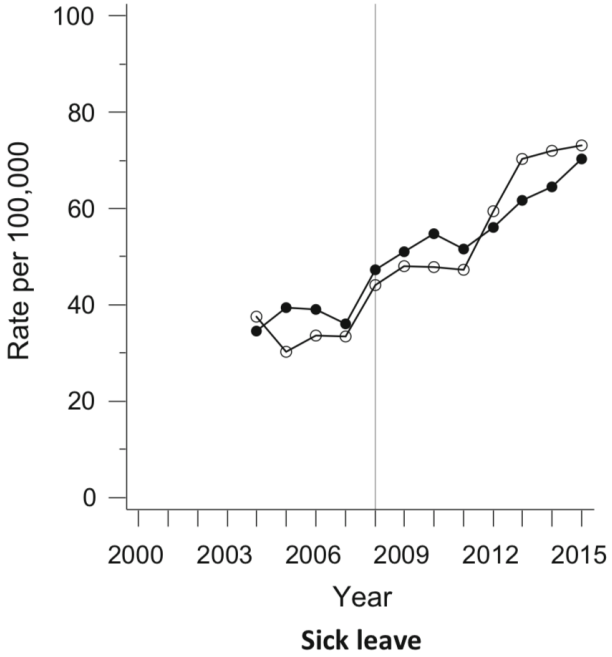
Stang et al 2018

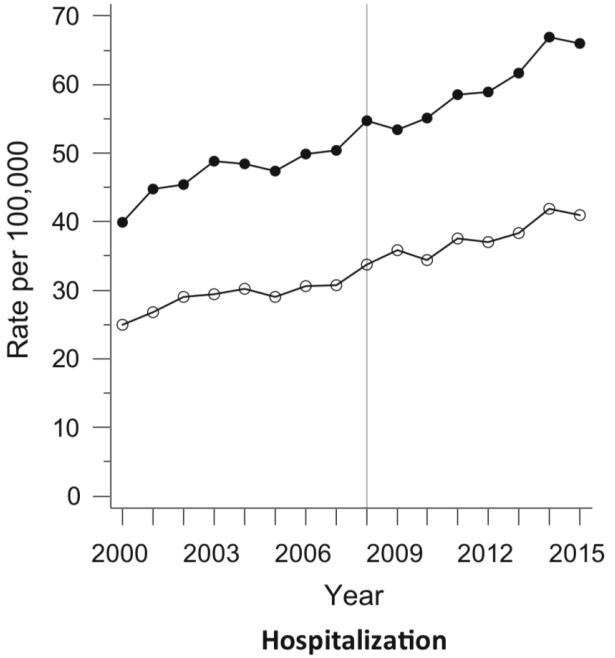
Non-melanoma data

North Rhine-Westphalia









Percentage change after screening

- BCC 22-66% (m) 38-87% (f)

- SCC 15-49% (m) 16-63% (f)

Brunssen et al. J Am Acad Dermatol. 2017

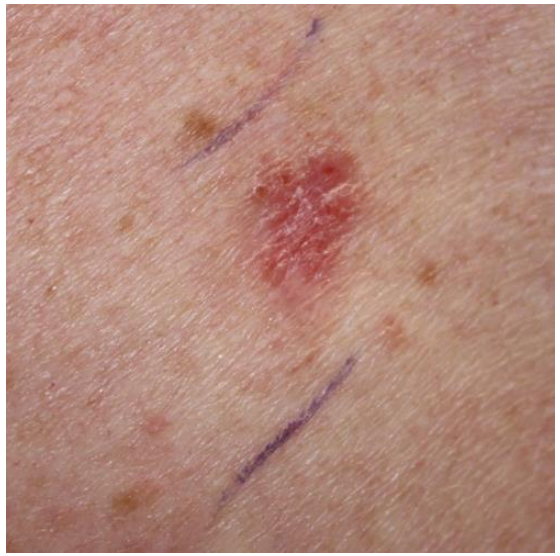
Stang et al. Eur J Epidemiology 2018: 33:303-12

- Number needed to screen to prevent 1 extra death of NMSC*

191 000 (vs 34 000 for MM)

*Assuming 50% risk reduction in screenees

BCC



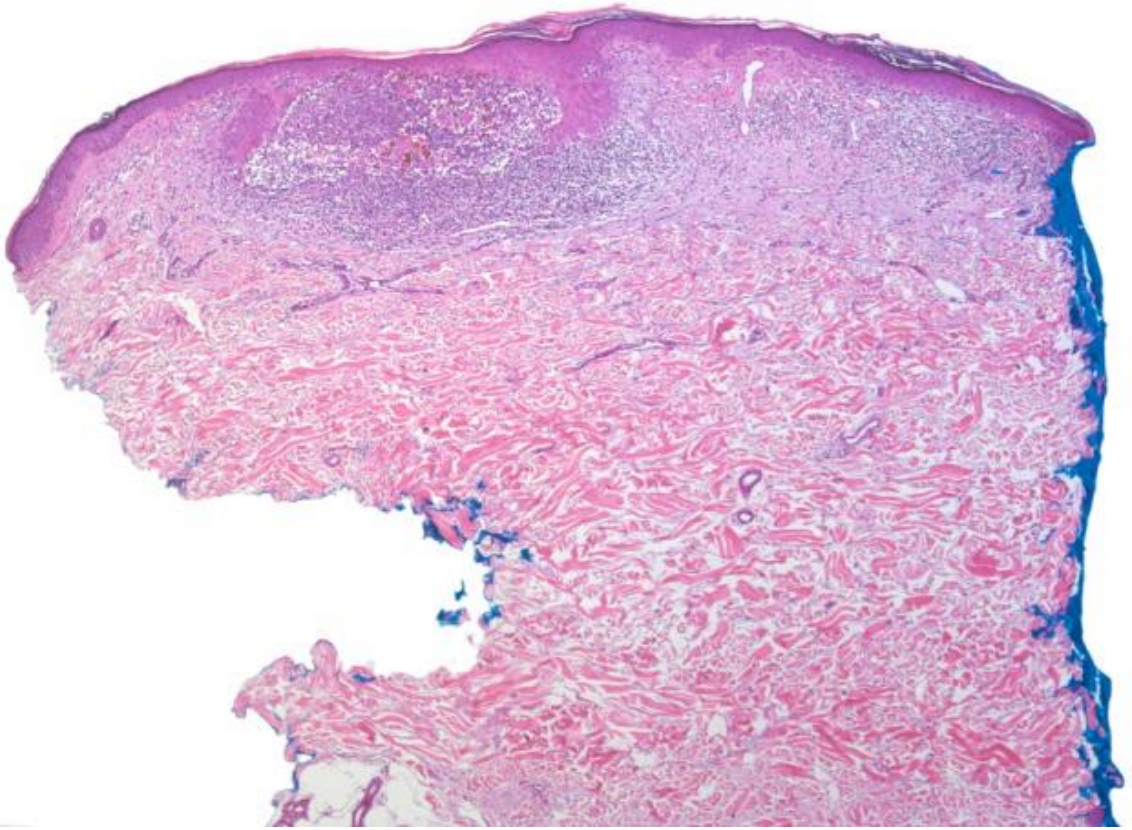
- Do not metastasize & No increase in all cause mortality
- Slow growing
  - Increase size 10% at 2-8 mo. and 81% at 5-10yrs
  - those treated 5-10yrs after first noticed only 6.6mm larger than those at first notice (Kricker JAAD 2014;70:456-)
- Largest associated with:
  - Older age & males
  - Ulceration, morpheaform, micronodular, superficial subtypes
  - <u>No skin checks</u>

Kricker et al. JAAD 2014;70:456-64
Wehner et al. JAAD 2018:78:663-72

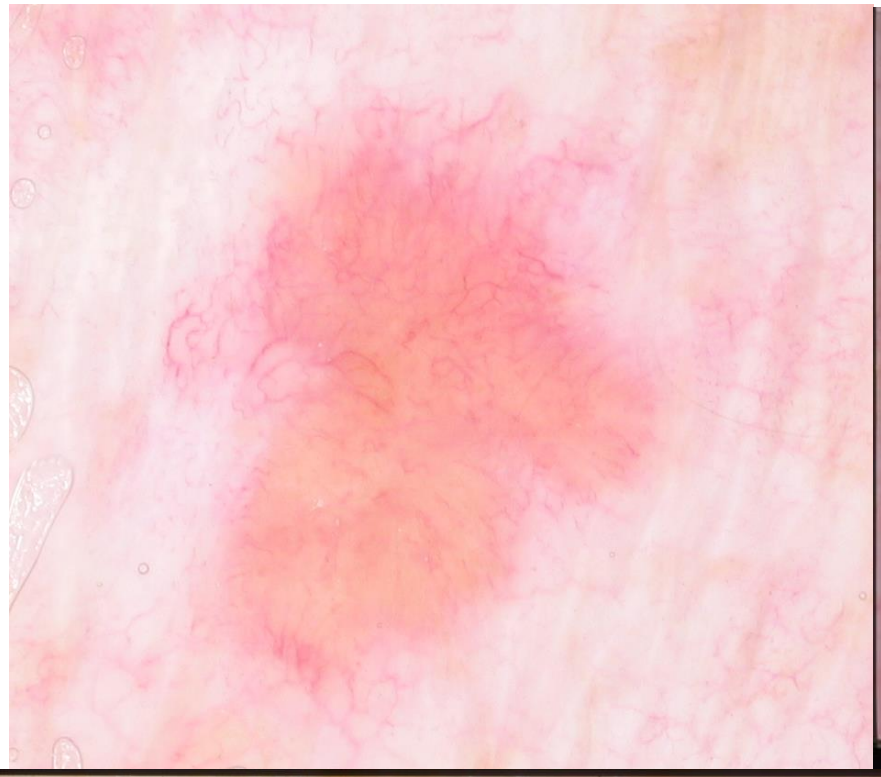
Screening for BCC?

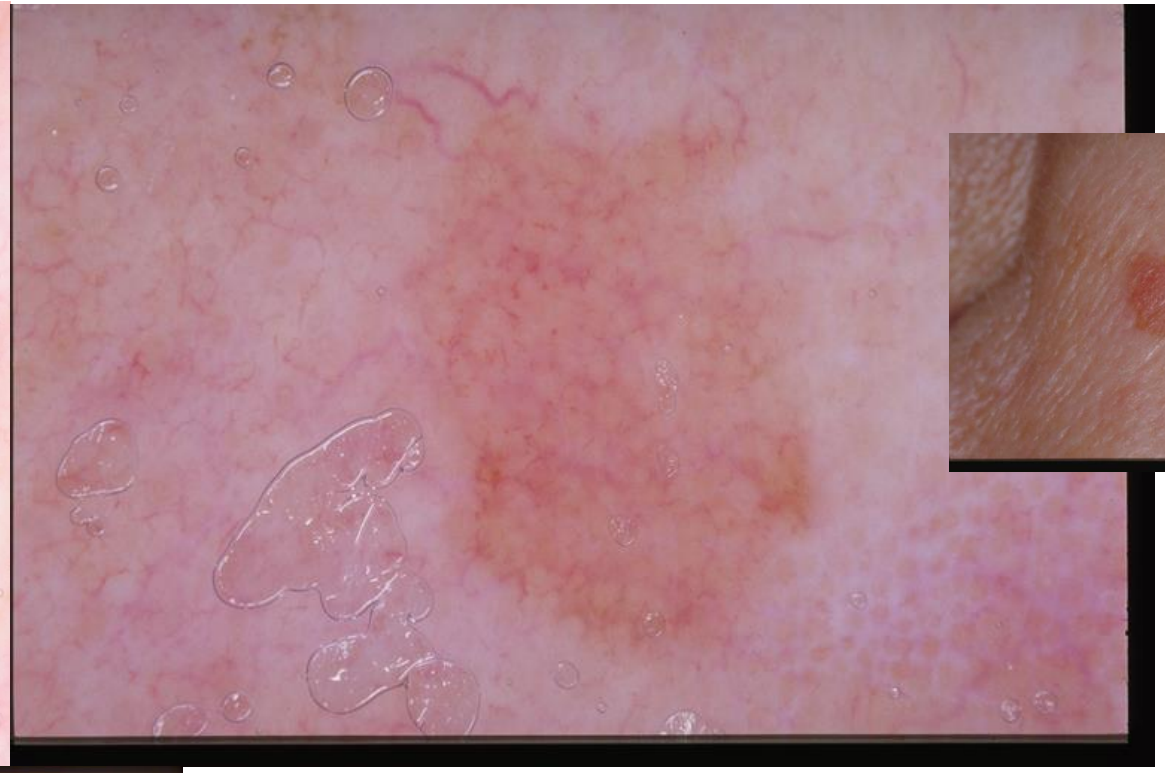
- ***Also undergo spontaneous regression*** Barnetson et al. Austral J Dermatol. 1997 38:S63-5;

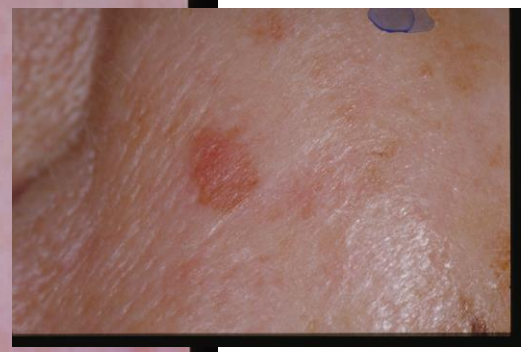
Regressing BCC Kulberg A et al. Dermatol. Pract. Concept. 2016;6:13-18

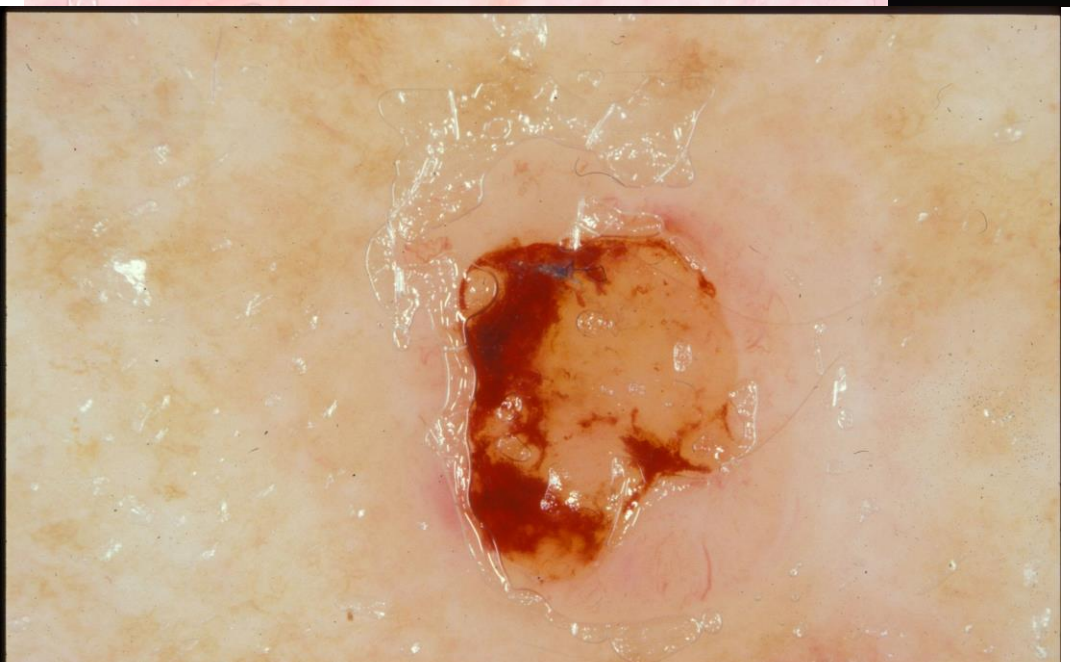


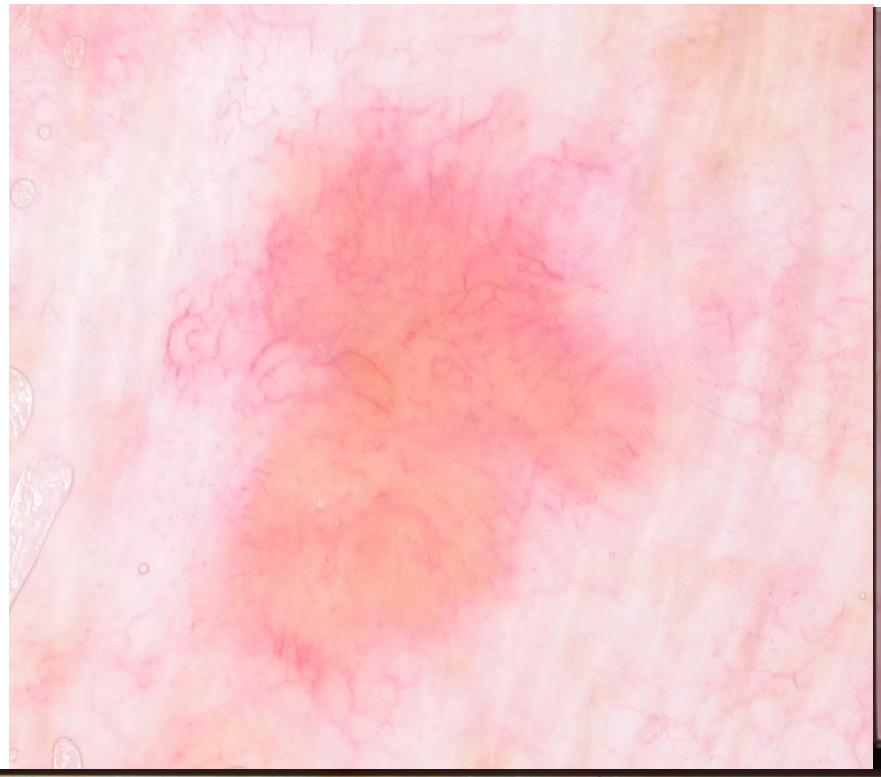
- 5% of histopathologically diagnosed lichenoid keratoses had BCC remnants after deeper sections

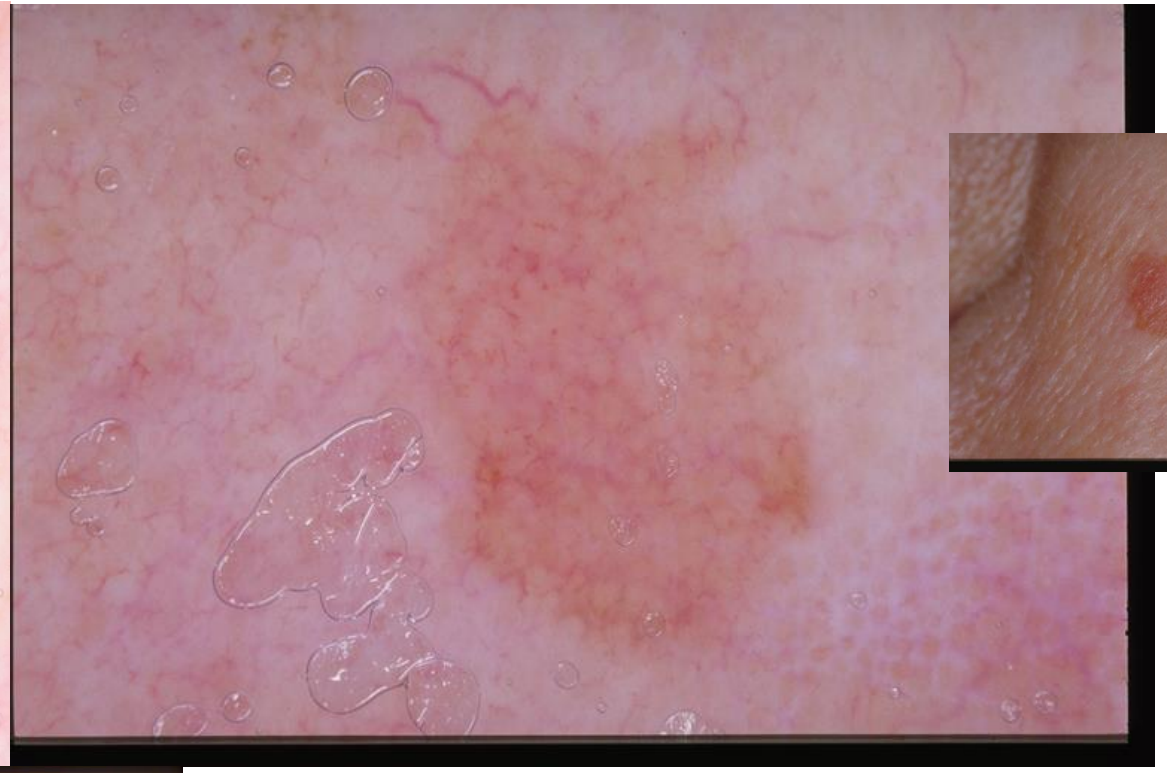


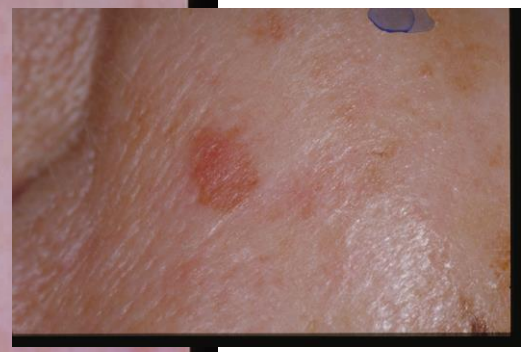


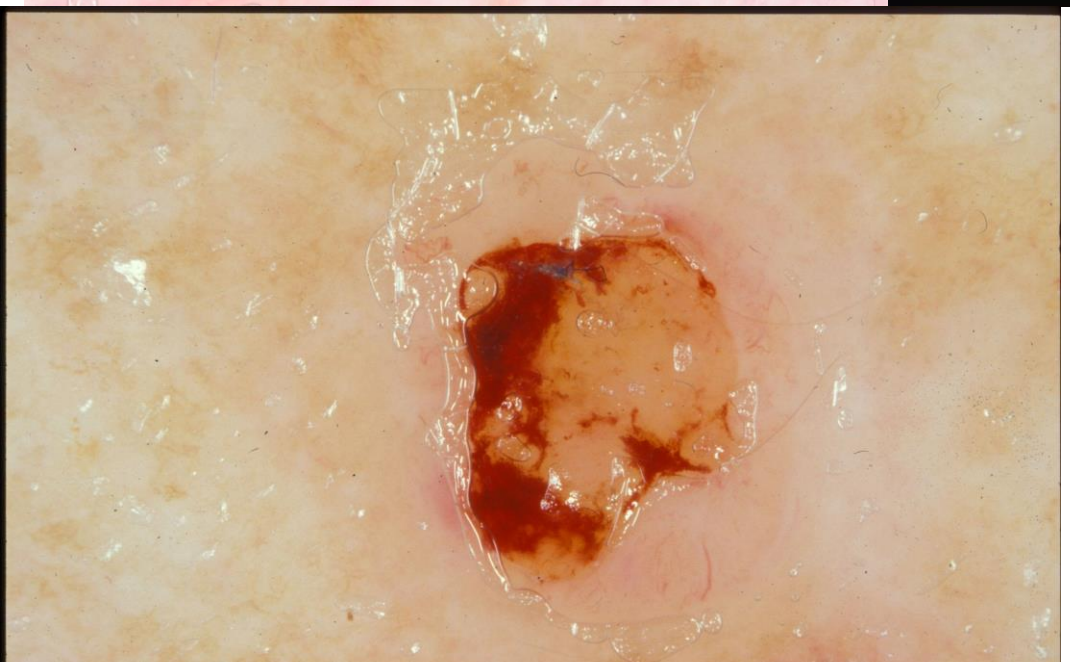












ALL INVASIVE

MELANOMA

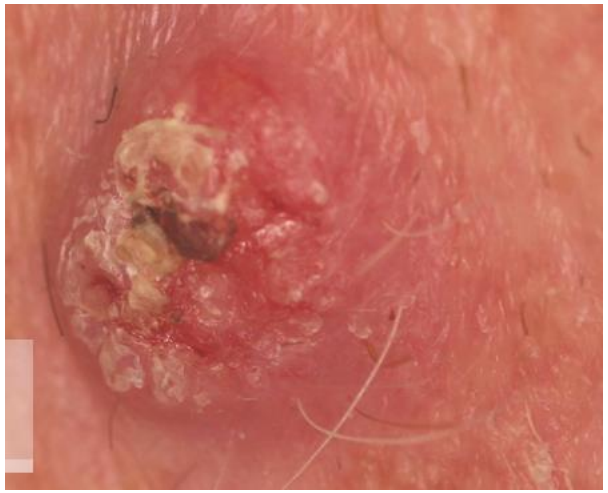
BCC mimics Amelanotic Melanoma

- Need to biopsy all

? Observe small flat low morbid lesions ➢ Quantify spontaneous regression

SCC

- Low mortality (age-adjusted mortality 1 per 100 000 person years*) &
- Increased *all cause* mortality RR 1.25
- Rapid evolution
- Large lesions
  - >2cm diam ; > 2mm depth
  - most significant risk of death
  - Associated with regular screening (1-3 mo.)
  - Male



Kricker et al. JAAD 2014;70:456-64
Wehner et al. JAAD 2018;78:663-72

* 180 per 100 000 person years for all cancer

If agree to Screen High Risk MM patients ONLY

- pre-malignant and NMSC lesions (RR = 4.28: 95%CI:2.80-6.55)

Gandini et al. Eur J Cancer 2005;41:2040-59

What to do with these lesions in screenees?

- NNT is an order of magnitude lower for NMSC vs Melanoma !

- US dermatologists
  - 1.9 (NMSC) vs 17.4 MM
  - 1.6 (NMSC) vs 15 MM

Nault A et al. JAMA Dermatol. 2015;151:899-902
Wilson R et al. J Dermatol. Treat 2012;23:65-9

Summary: Acceptable absolutes

- 20% reduction in mortality adults
- Reduce NNS by targeting high risk individuals
- Reduction in absolute no.s of > T1a MM* *T1a < 0.8 mm non-ulcerative
  - Total population & inter-screening tumours
- Reduce NNT by using dermoscopy & dermoscopy monitoring (improves sensitivity)
- Negative psychosocial consequences & overdiagnosis quantify
- Treat all SCC
- Biopsy all BCC
  - ? Observe small flat low morbid lesions ➢ Quantify spontaneous regression