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So Who is Really at High Risk of Melanoma and What is their Risk? - Concurrent Workshop Repeated

Saturday, 17 August 2013	Start 2:00pm	Duration: 55mins	Pyramids
	Start 3:05pm	Duration: 55mins	Pyramids

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Measuring risk. Using melanoma in New Zealand as an example.

Dr. Mary Jane Sneyd
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"And it was so typically brilliant of you to have invited an epidemiologist."

An extract from some NZ advertising which I've paraphrased.

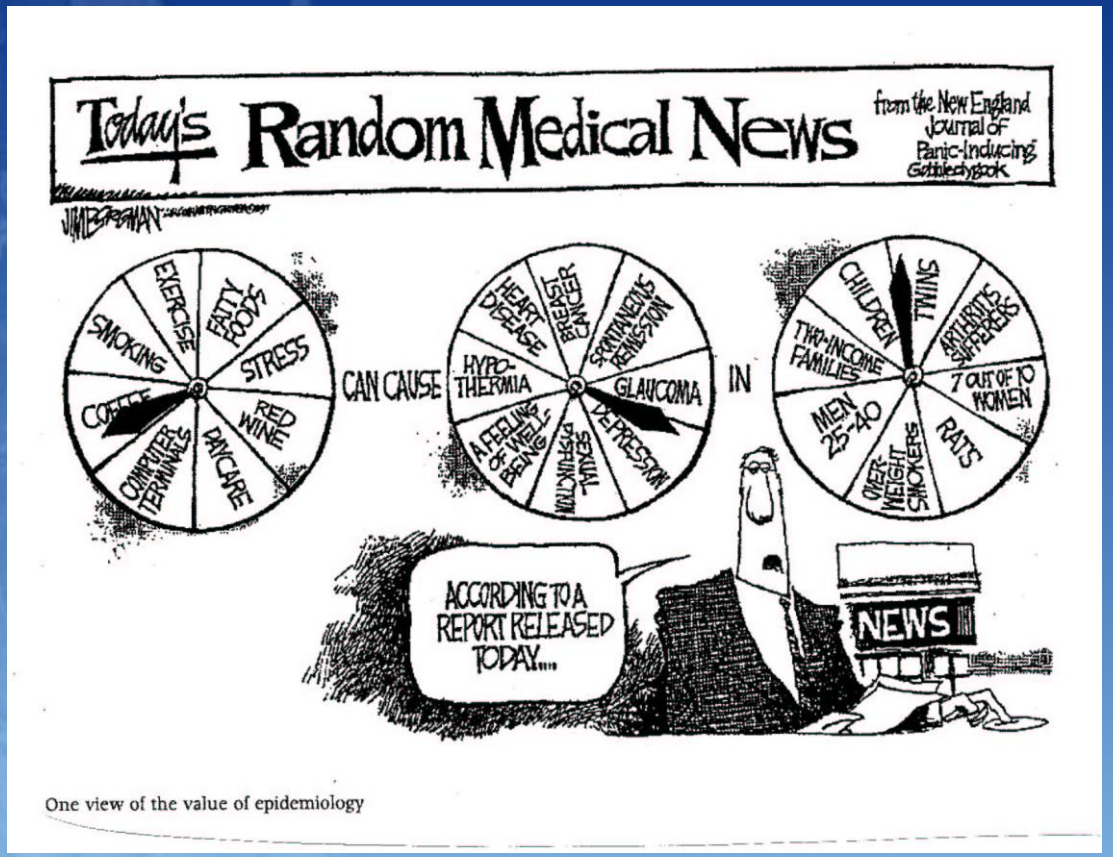
We are correctly attracting people at high risk of melanoma – 90% of attendees have at least one risk factor for melanoma. Average age of attendees is 40 yrs.

Definitions 1

- Epidemiology

  =study of disease patterns among populations in time and space.

  = tool for the assessment of risk.



One view of the value of epidemiology

Definitions 2

- What is meant by risk?

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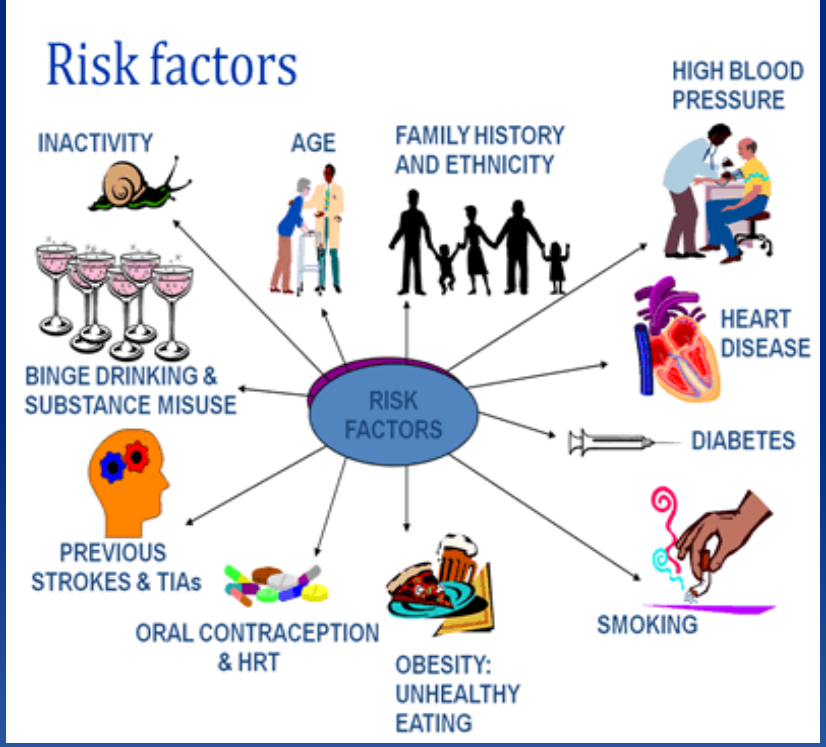
- What is meant by risk?
  - **Risk** is the **probability** or **chance** that an event will occur within a specified time.
  - Often used to express the probability that a particular outcome will occur after a certain exposure.
  - Therefore expressed as a % or proportion (and sometimes a ratio or fraction). Must be between 0-100% (or 0-1 as a proportion).

Definitions 3

- **What is a risk factor?**

Definitions 3 cont'd



- **What is a risk factor?**
  - On the basis of epidemiological evidence, an exposure that is statistically associated with an outcome. Eg having pale skin is a risk factor for melanoma.
  - A risk factor does not necessarily CAUSE the outcome of interest. Eg having a history of NMSC is a non-causal risk factor for melanoma.

Measures of risk

- Absolute risk – this is the measure that is most useful in clinical practice.
  - the probability that an outcome will occur in a specified time. Usually expressed as % or proportion (from 0-1) or ratio or fraction.
  - Eg the absolute risk/chance of patient X developing melanoma in the next 5 years is 1%.
  - Sometimes expressed as a categorical risk score (this is NOT a count of risk factors).

Measures of risk cont'd

- HOWEVER, the most commonly seen measure of risk in the clinical literature – the relative risk- can be very misleading.
- **Relative risk** – is a comparative measure. It compares the probability of an outcome in one group of patients with another specified group of patients.
  - It DOES NOT predict the probability of the disease occurring. It tells you nothing about the chance that your patient will develop disease.
  - It IS very important if studying causes of disease.
  - e.g. the RR of melanoma in people with >100 moles is ~7 x people with 0-15 moles.
- You need to ask yourself – is this risk measure giving me the probability of developing the outcome? Or is it a comparison between 2 (or more) groups of people? Or something else?

Measures of risk cont'd

- Other measures you will see-
- Lifetime risk (cumulative incidence) – By definition, it is measured from birth to age 74 yrs. Assumes that melanoma incidence not changing over a lifetime. Very limited clinical use.
  - e.g. lifetime cum incid of melanoma in men 4.3% and women 3.3%.
  - Whereas at age 50, risk of melanoma to age 74 in men is 3.6% and in women, 2.5%

Measures of risk cont'd

•Average risk – This term is bandied around a lot in clinical literature, but what does it mean? The risk for an 'average' person? The overall risk of melanoma? The median absolute risk?

- In 2009, the overall chance of developing invasive melanoma in New Zealand in one year was approximately 2212/4,000,000 (the crude incidence rate) or 0.00055 or 0.05%.
- Again, this risk measure is not helpful as risk varies enormously by age and sex (and other things).
  - Eg, in 2009 it ranged from 0% for 10yr old girls to 0.33% in 80 yr old men.

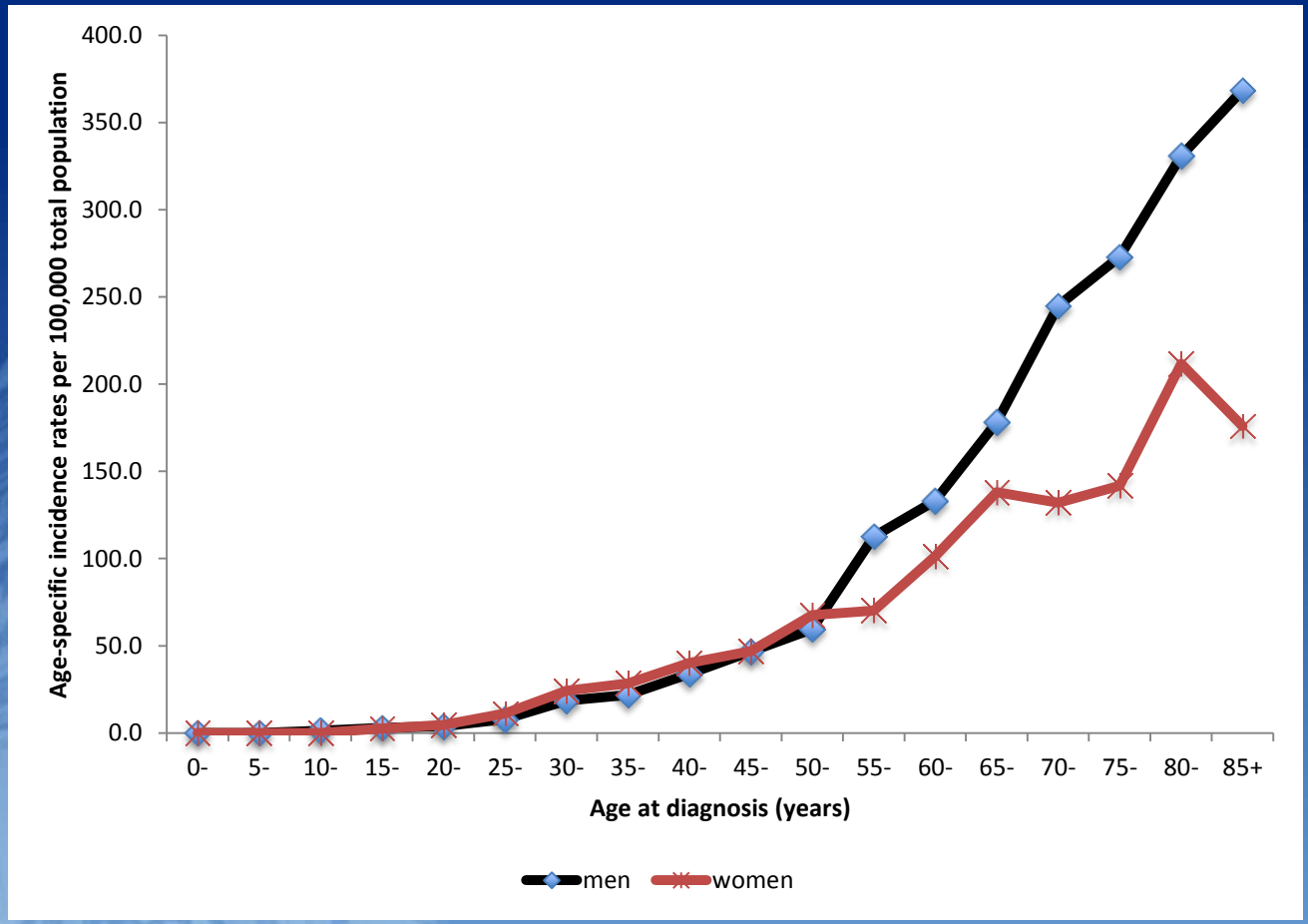
•Attributable risk. A measure of how much disease is due to a certain exposure.

- Gives % of disease prevented (ideally) if exposure eliminated. Useful for public health interventions and assessing priorities for public health action at population level.

Melanoma in New Zealanders in 2009

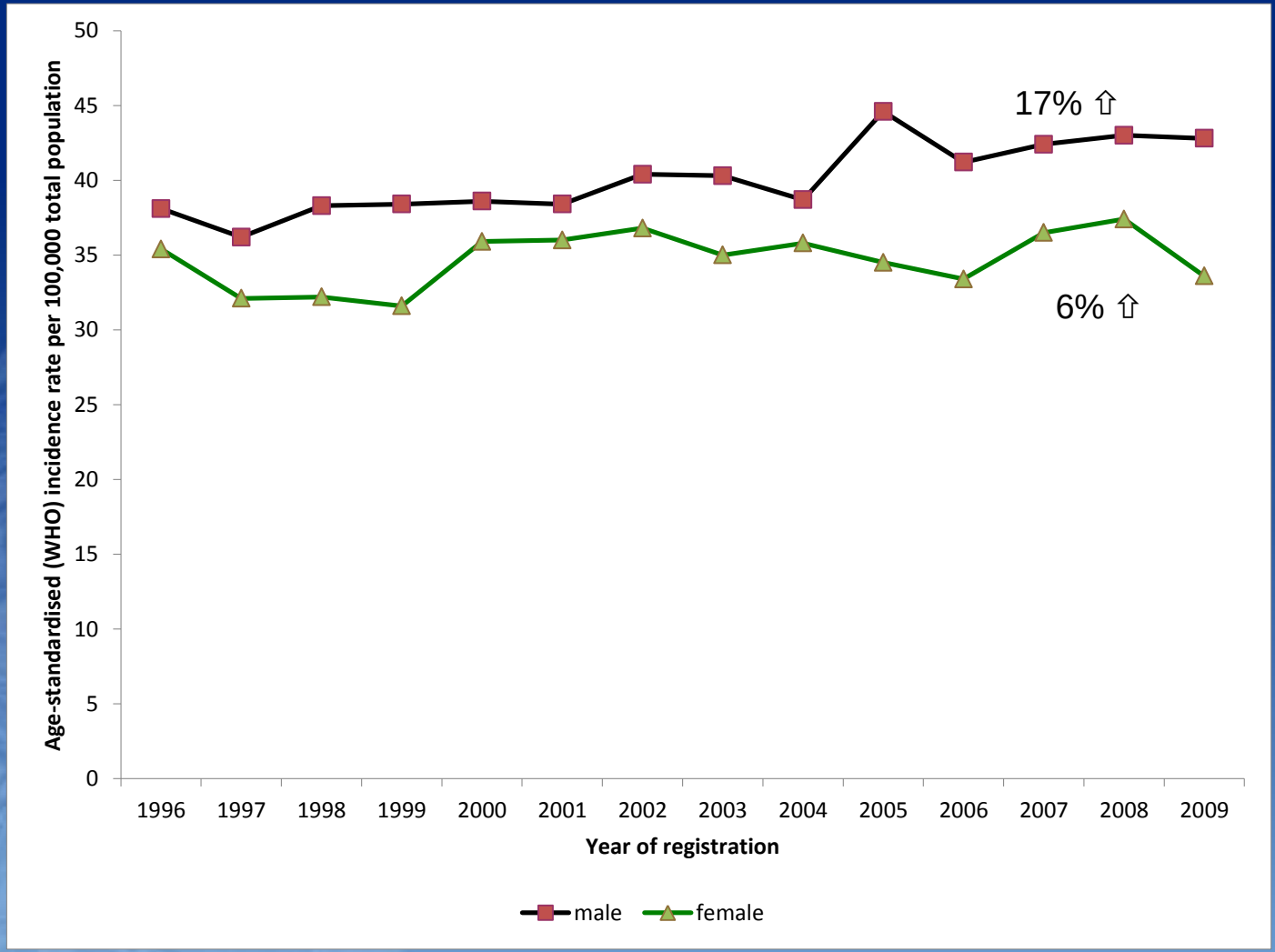
- 4th highest cancer registration rate overall.
- 2212 new people registered with melanoma (including 21 Maori and 8 Pacific peoples)
- Age-standardised registration rate per 100,000 total population: 42.8 in men, 33.6 in women.
- Cancer very rare in young people but melanoma 2nd most commonly registered cancer in females aged 0-24 years (after breast cancer).
- 326 people died of melanoma (including 7 Maori and 3 Pacific peoples)
- Age-standardised mortality rate per 100,000 total population: 7.2 in men, 3.3 in women

Age-specific incidence rate of melanoma in New Zealand by sex, for 2009.

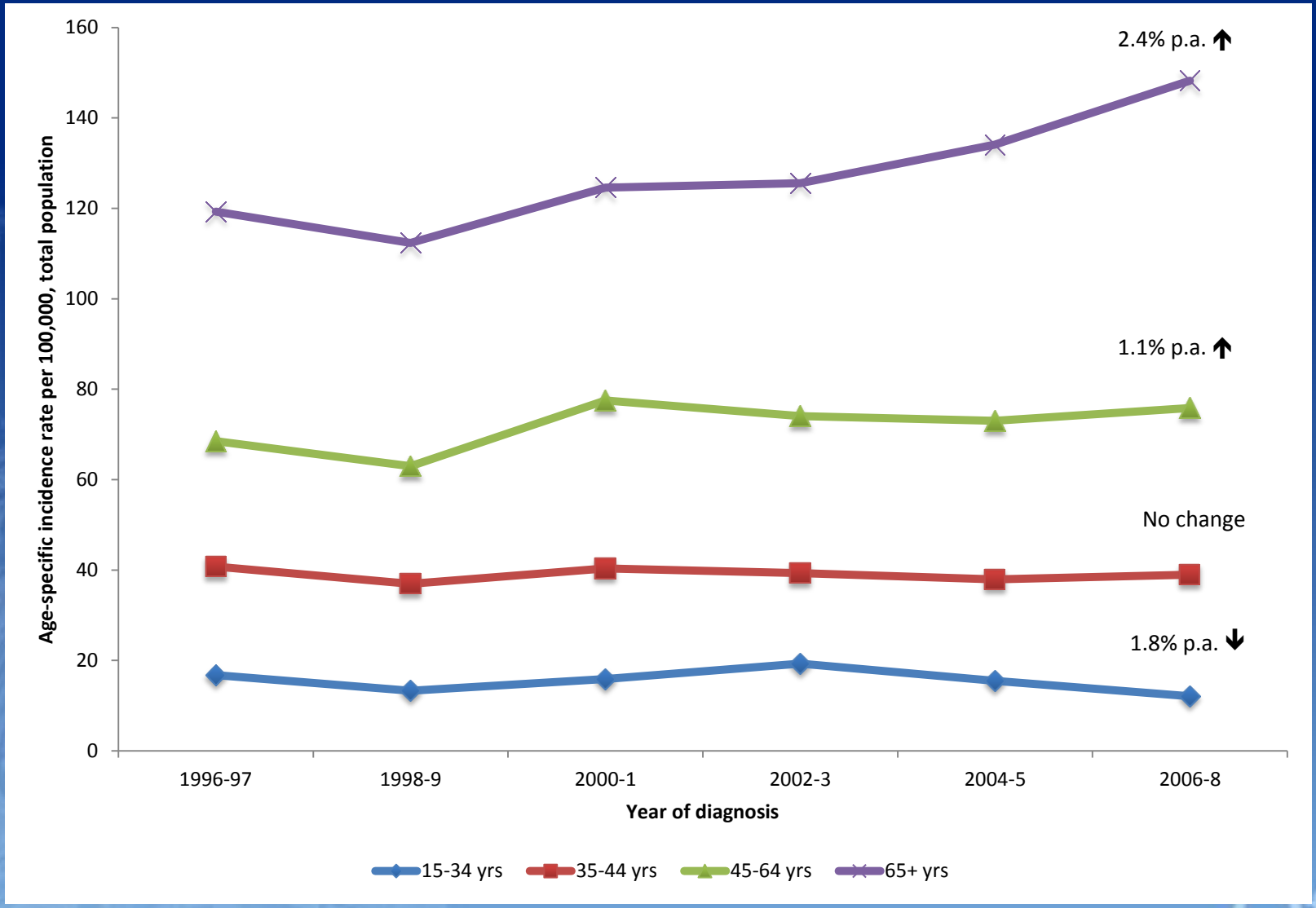


•Study for Cancer Society: 37% of people >65 years thought they were at much lower risk of skin cancer than younger people.

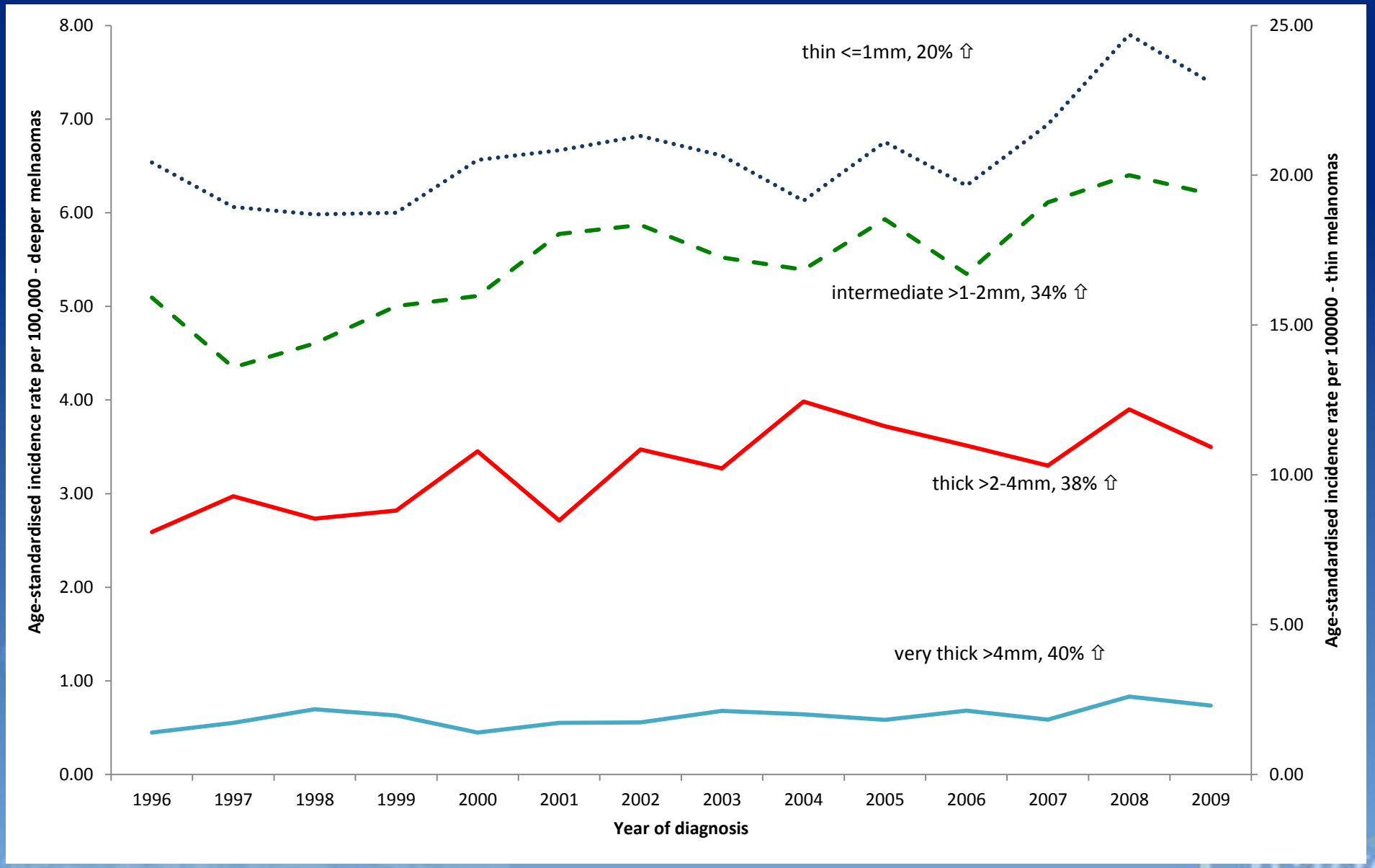
Age-standardised incidence rate of melanoma in New Zealand for the total population, 1996-2009.



Age-specific incidence rate of melanoma for the total female population, 1996/7 to 2006/8.*

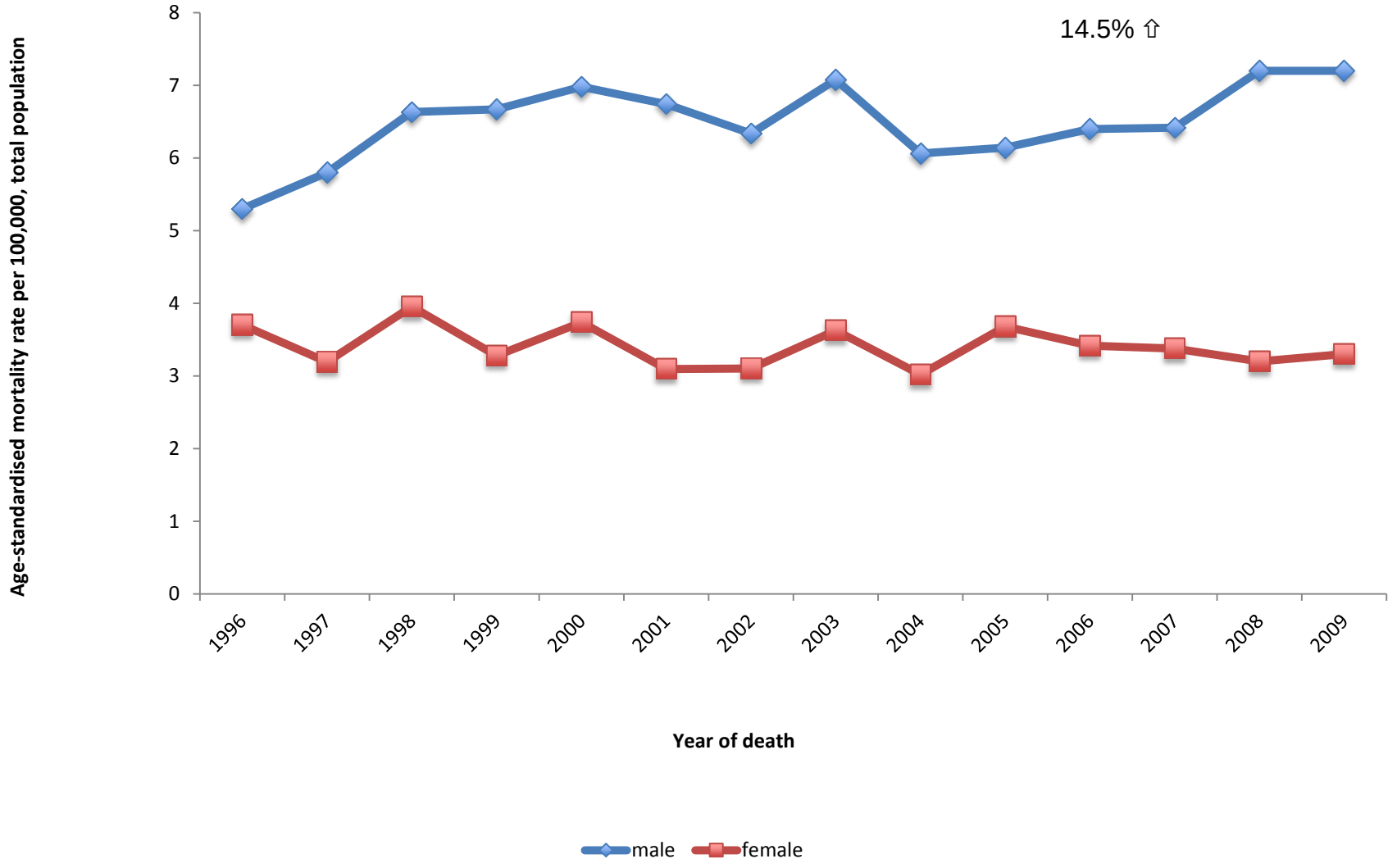


Age-standardised* incidence rate of melanoma by depth category.



*using Segi standard

Age-standardised (WHO) mortality rate of melanoma in New Zealand, 1996-2009.



So what now?

Ideally want to prevent melanomas or diagnose them while still thin.

- Targeting prevention, early diagnosis, and surveillance to people at higher risk (greater chance of developing melanoma) is the approach being taken internationally to achieve this.
- This individualisation follows the direction that medicine and some screening is taking worldwide.

BUT

- first have to accurately identify people at high risk.

How to define ‘high risk’?
What is ‘high’?

- Could be defined as top 10% of absolute risk.
- Or over a threshold of risk, say >1% probability of developing melanoma in 5 years.

- It **doesn’t** mean that the ‘high risk group’ are at higher than **average** (whatever this is) or median risk – this is 50% of the population!
- It **doesn’t** mean that groups of people with (relative) risk >4 have a high probability of developing melanoma.

- If it is said that people with red hair have a higher risk of melanoma, what does this mean?

- If it is said that people with red hair have a higher risk of melanoma, what does this mean?
  - It does NOT mean that people with red hair have higher than ‘average’ risk.
  - It does NOT mean that all people with red hair are at high risk (ie top 10% of risk) of developing melanoma.
  - It DOES mean that, all other things being equal, people with red hair have a higher risk of melanoma *than people with other hair colours.*
    - Ie a relative measure of risk

Measuring individual risk

Targetting prevention and early detection allows more intensive participation in prevention and early detection activities by people identified at high risk.

Therefore we need a measure of absolute risk for an individual to determine who is at low, medium and high risk.

As many interrelated factors are associated with the chance of getting melanoma, a mathematical model is needed as the computation can't be done in your head.

However, although Relative Risk is the most common measure of risk in the literature it is a **comparative** measure, **not** the probability of an event occurring. So is no use in estimating the risk for individuals.

So who has the highest 5-yr risk of developing melanoma?

Patient A, 60 yr old man, lives in the Southern region, fair skin, history of NMSC, 5 big moles, outdoor occupation<age 18yrs.

Patient B, 80 yr old woman, lives in the Midland region, olive skin, no large moles.

Patient C, 40 yr old woman, lives in the Midland region, fair skin, 4 large moles, family also has large moles, history of NMSC.

Patient D, 20 yr old man, lives in the Central region, red hair, history of NMSC, 1 big mole.

Patient A, 60 yr old man, lives in the Southern region, fair skin, history of NMSC, 5 big moles, outdoor occupation<age 18yrs.

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Patient C, 40 yr old woman, lives in the Midland region, fair skin, 4 large moles, family also has large moles, history of NMSC.

Patient D, 20 yr old man, lives in the Central region, red hair, history of NMSC, 1 big mole.

Patient C has highest 5 year risk, ~6%

Then Patient A, ~5%

Then Patient B, ~0.08%

Patient D has lowest risk, ~0.05%.

What is the problem with this NZ advertising which I've paraphrased?

We are correctly attracting people at high risk of melanoma – 90% of attendees have at least one risk factor for melanoma. Average age of attendees is 40 yrs.

Absolute risk of melanoma in 5 years, as %

	age in years	20	40	60	80
no risk factors	olive skin, no large moles	0.01	0.02	0.04	0.05
1 RF	hx of NMSC	0.03	0.09	0.15	0.2
1 RF	fair skin	0.04	0.11	0.18	0.24
2 RF	fair skin, 2 large moles	0.1	0.31	0.51	0.68
2 RF	hx NMSC, 3+ large moles	0.13	0.39	0.64	0.86
2 RF	fair skin, 3+ large moles	0.15	0.47	0.77	1.04
3 RF	medium skin, 2 large moles, fam hx dysplastic moles	0.16	0.49	0.8	1.07
3 RF	fair skin, 1 large mole, hx NMSC	0.18	0.56	0.91	1.22
3 RF	fair skin, 3+ moles, fam hx dysplastc moles	0.4	1.23	2.01	2.69
4 RF	fair skin, 3+ large moles, family hx dysplastic naevi, personal history NMSC	1.47	4.55	7.32	9.69

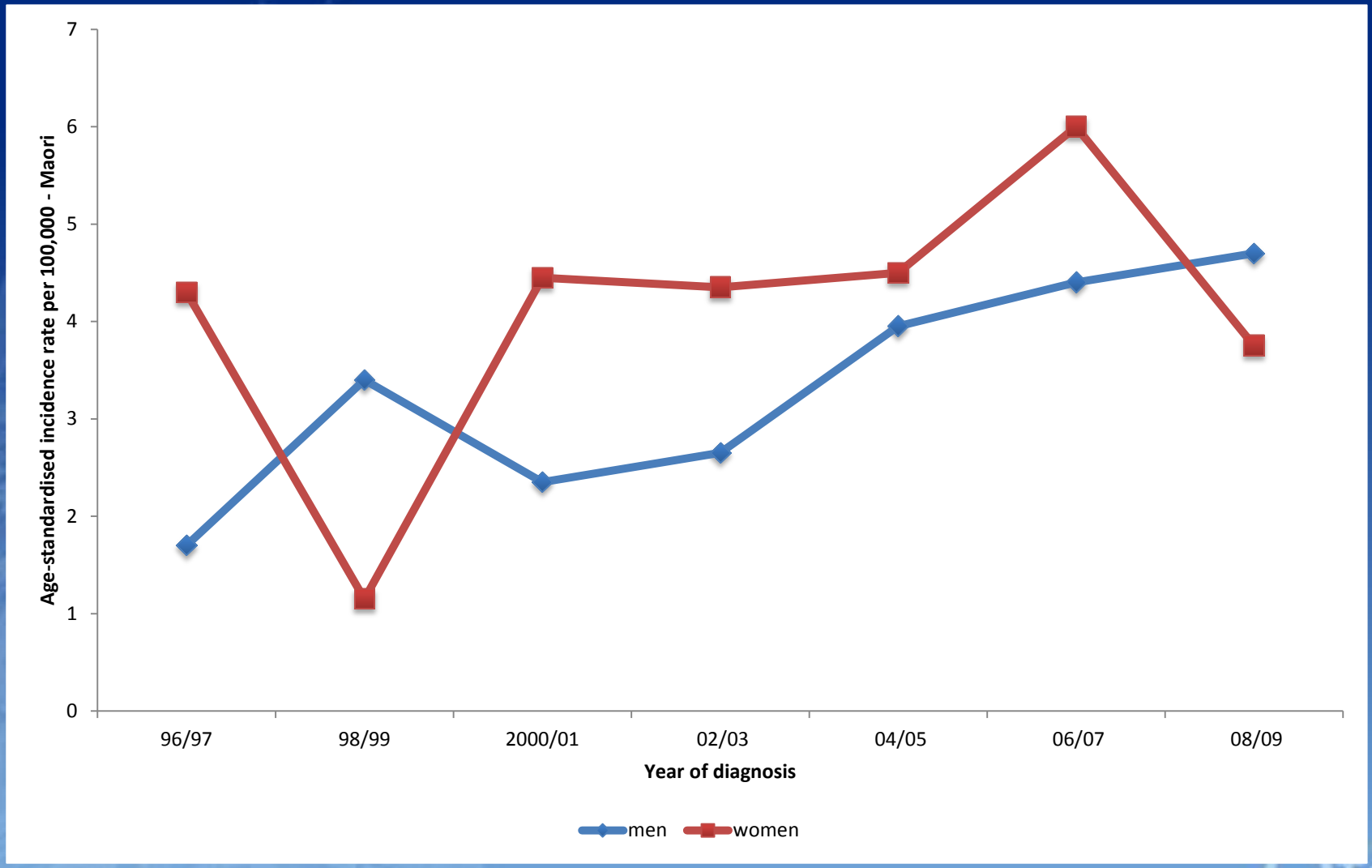
high risk >=1% in 5 yrs

medium risk >0.5-1% in 5

Melanoma risk predictor model

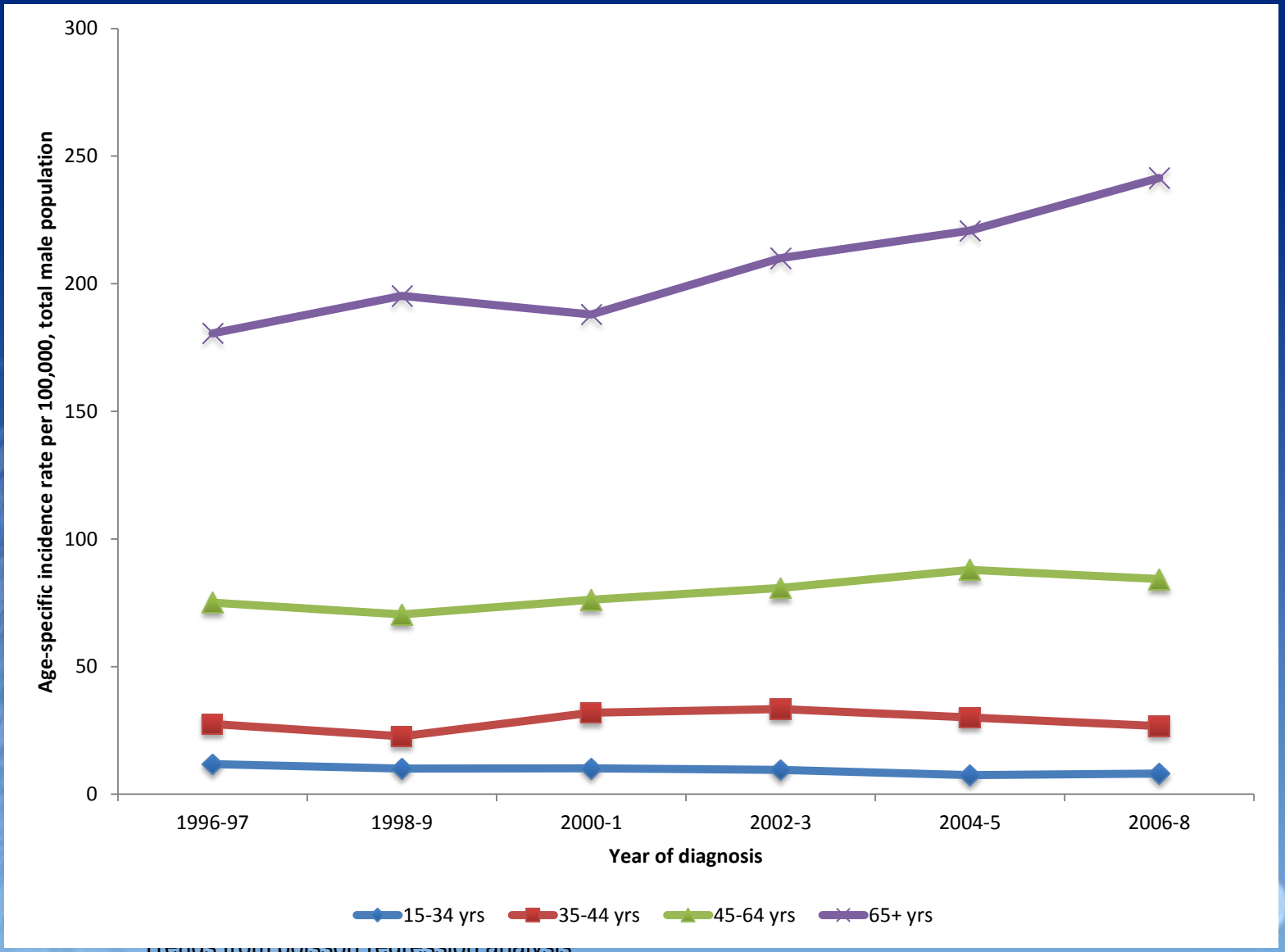
- The melanoma risk predictor model allows you to estimate the absolute risk for individual patients based on their risk factors for melanoma.
- Only then can you plan (and trial) management strategies to offer your patient.

Age-standardised incidence rate of melanoma in New Zealand for Maori, 1996/7-2008/9.*



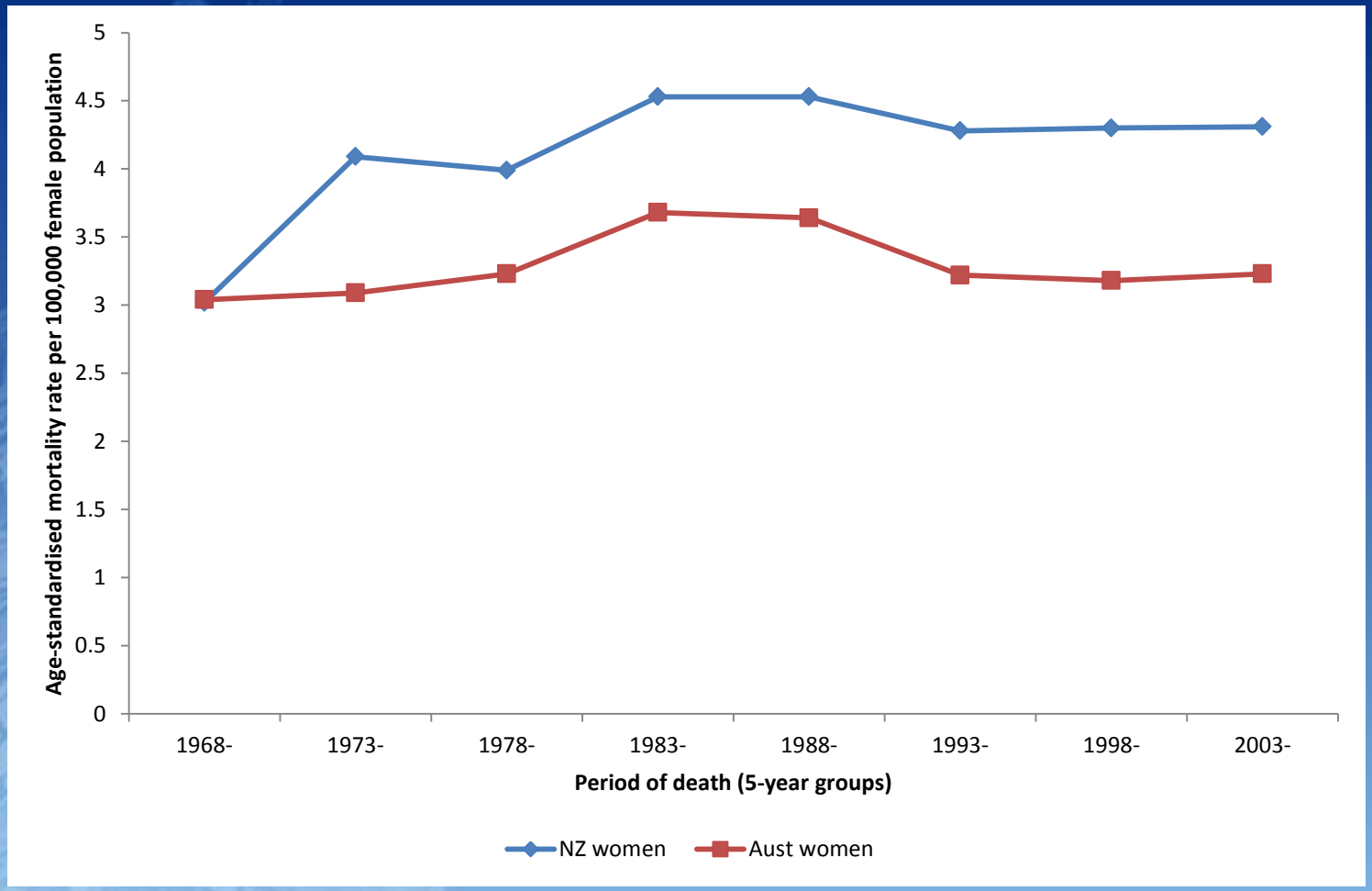
* Data from publications of the NZ Cancer Registry, recalculated to the Segi standard.

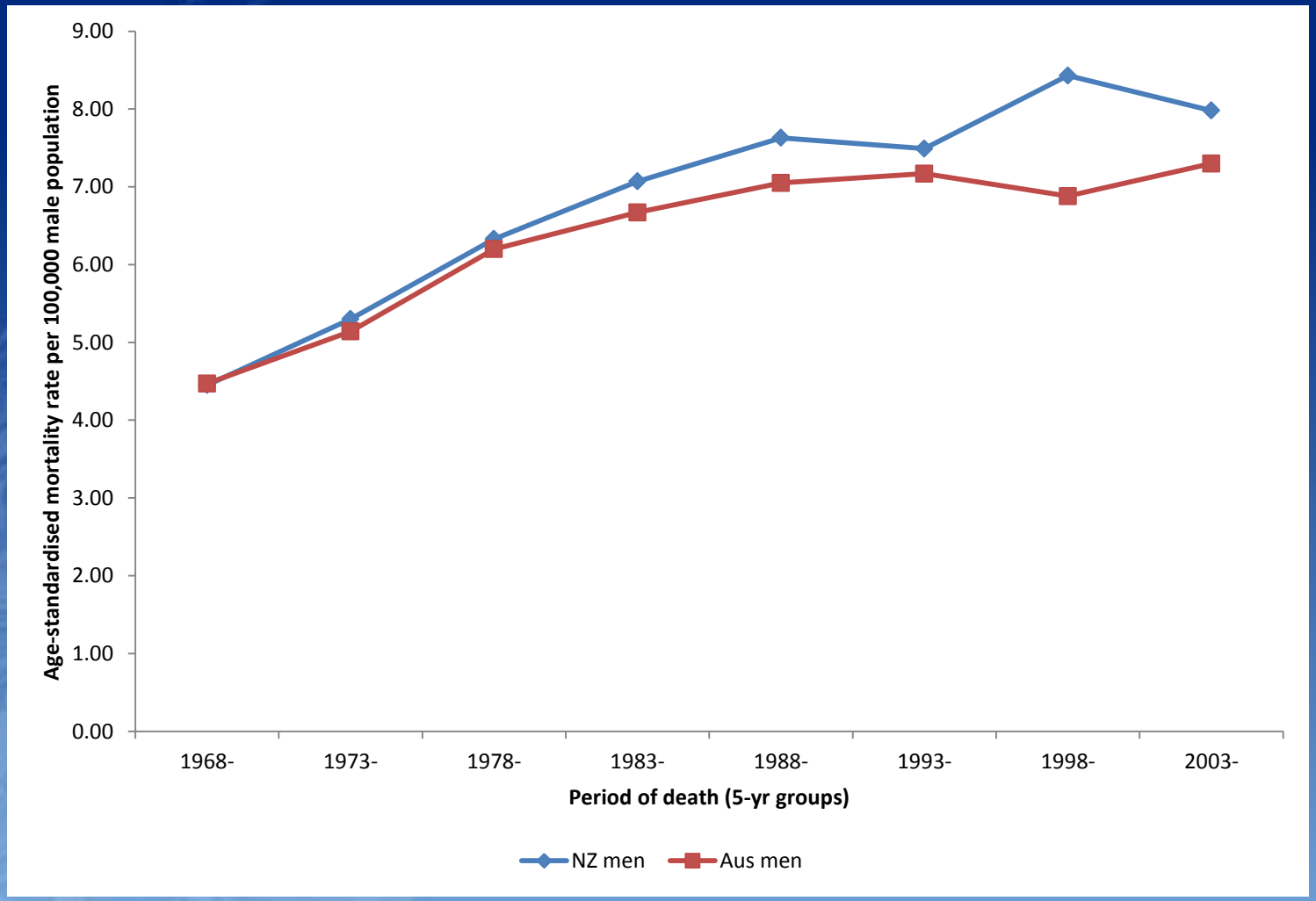
Age-specific incidence rate of melanoma for the total male population, 1996/7 to 2006/8.*

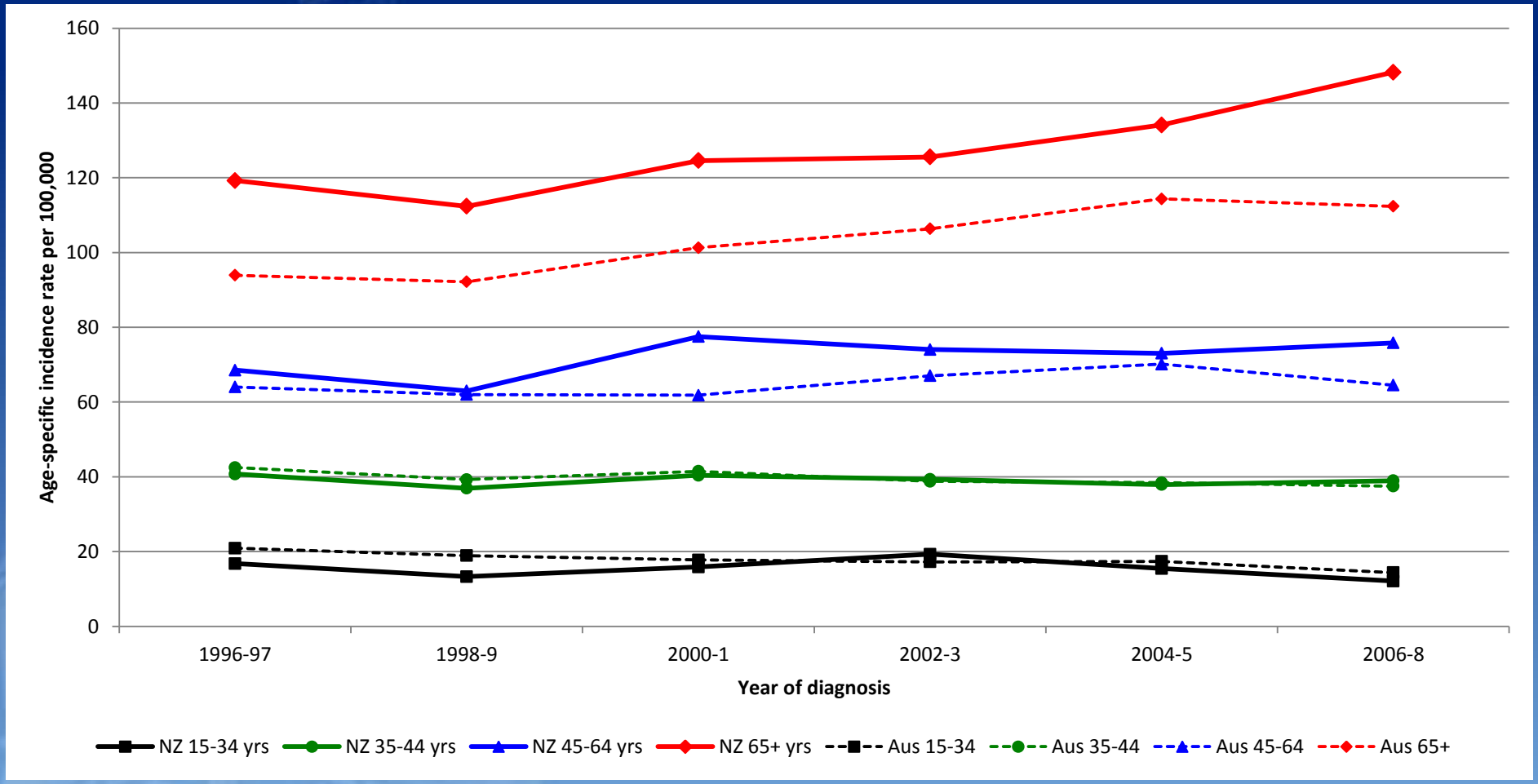


Trends from poisson regression analysis

Comparison of age-standardised mortality rates for melanoma in New Zealand and Australian women, 1968/72-2003/7.




9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Age-standardised mortality rate per 100,000 male population
1968-
1973-
1978-
1983-
1988-
1993-
1998-
2003-
Period of death (5-yr groups)
NZ men
Aus men


160
140
120
100
80
60
40
20
0
Age-specific incidence rate per 100,000
1996-97
1998-9
2000-1
2002-3
2004-5
2006-8
Year of diagnosis
NZ 15-34 yrs
NZ 35-44 yrs
NZ 45-64 yrs
NZ 65+ yrs
Aus 15-34
Aus 35-44
Aus 45-64
Aus 65+

Risk factors for developing the first melanoma and associated RR.

From International data.

Ethnicity non-Maori vs Maori	9
>100 moles vs 0-15 moles	6.8
>5 atypical moles vs no atypical moles	6.5
History of pre-malignant & NMSC vs none	4
Transplantation/immune suppression	2
Fair skin vs dark	1.7
Family history vs none	1.7
History of sunburns vs no sunburns	1.6
Intermittent excessive sun exposure vs none	1.3

Population attributable risk (PAR%) vs RR.

From univariate analysis of international data.

Risk factor	PAR%	RR
>100 common moles	43	6.8
>5 dysplastic moles	35	6.5
History of NMSC	31	2
Fair skin	25	1.7
Sunburn with blisters	23	1.6
Family history	2.2	1.7
Immune suppression	0.5	2

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Advantages of risk predictor models for estimation of absolute risk.

- Can assess multiple risk factors.
- Not just a (relative) risk factor list – no use for identifying people at high risk. Doesn't tell us what their risk is.
- Not restricted to predicting disease development – used for predicting prognosis, predicting/evaluating outcome of therapy.
- Can better target strategies to reduce disease risk or encourage earlier diagnosis (e.g. for melanoma) in individuals.
- Can be updated as more data (eg genetic info) becomes available.
- Other predictive tools already available e.g. for breast cancer and for CVD.

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Melanoma case-control study, 1992-1994.

- Cases-histological diagnosis of in-situ or invasive melanoma, on eroll.
- Controls- random selection from eroll, no melanoma, frequency matched on age and region.
- Aged 20-79 years.
- Restricted to white-skinned people of European descent.
- 3 regions of NZ- Hawkes Bay, Bay of Plenty, Nelson-Marlborough.
- Data collected by telephone interview.
- Information collected on self-reported demographics, phenotype, mole counts, skin examinations, sun exposure, occupation, medical history, family history.
- Participants - 368 cases, 270 controls.
- → OR of association between risk factors and melanoma.

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Divergent pathway hypothesis.

More recent evidence -melanomas occurring on sun-exposed or non sun-exposed body sites arise from different causal pathways.

Predicts that melanomas developing in people with few naevi, i.e. with a low propensity for melanocyte proliferation, will arise on chronically sun-exposed sites.

These melanomas tend to be LM, and occur in older people with a history of sun damage to skin and NMSC.

But people with many naevi will tend to develop melanomas on sites with high naevi counts on intermittently sun-exposed sites –

these melanomas tend to be superficial spreading melanoma (SSM) or NM.

This divergent hypothesis has not yet been explored in NZ.

Absolute risk of melanoma in 5 years, as %

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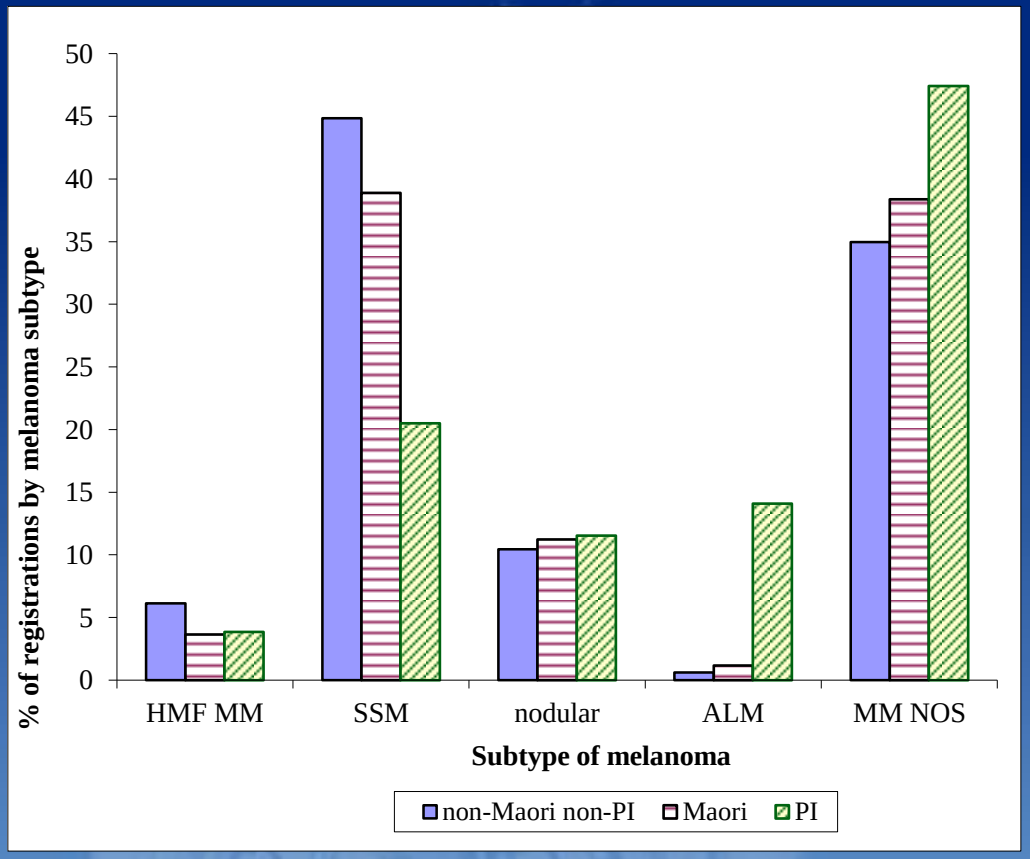
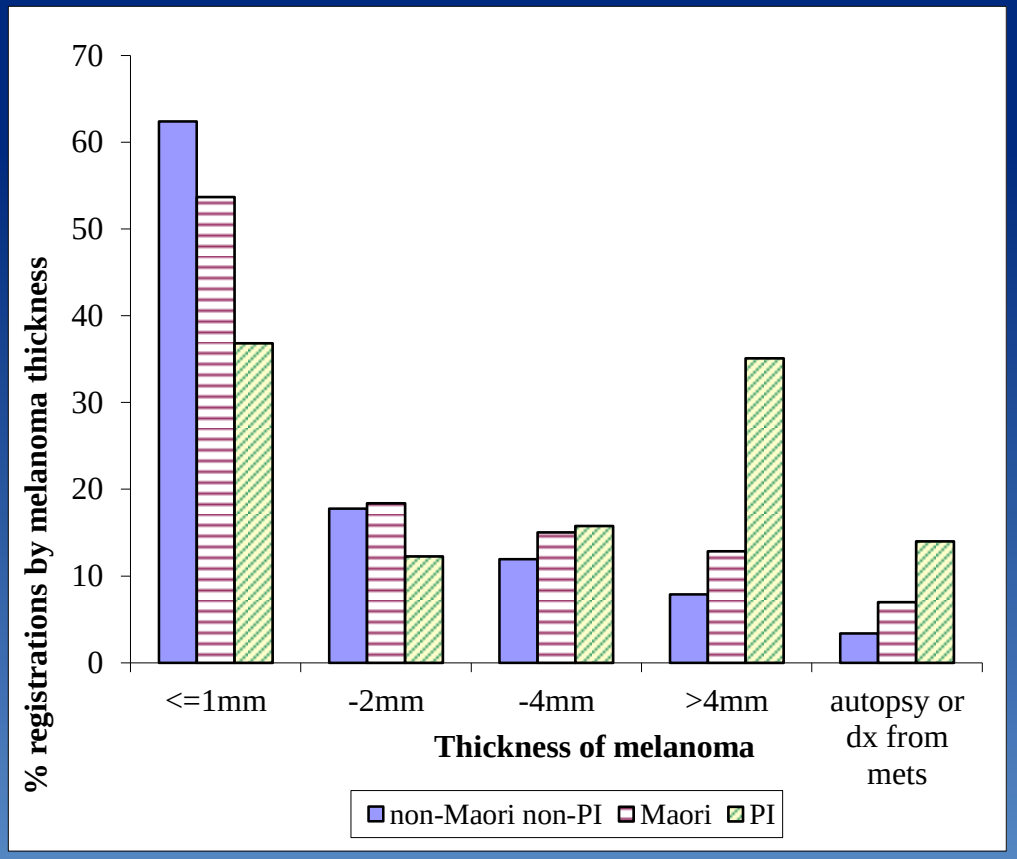
high risk= top 10% of risk

medium risk =next 15% of risk

Thickness and subtype by ethnic group, 1996-2010





HMF – Hutchinson's melanotic freckle
SSM – superficial spreading melanoma
Nodular – nodular melanoma
ALM – acral lentiginous melanoma
MM NOS – malignant melanoma not otherwise specified