Otago Spotlight Series
Cancer Research

Inequalities in testicular cancer:

A mystery to be solved

Dr Jason Gurney

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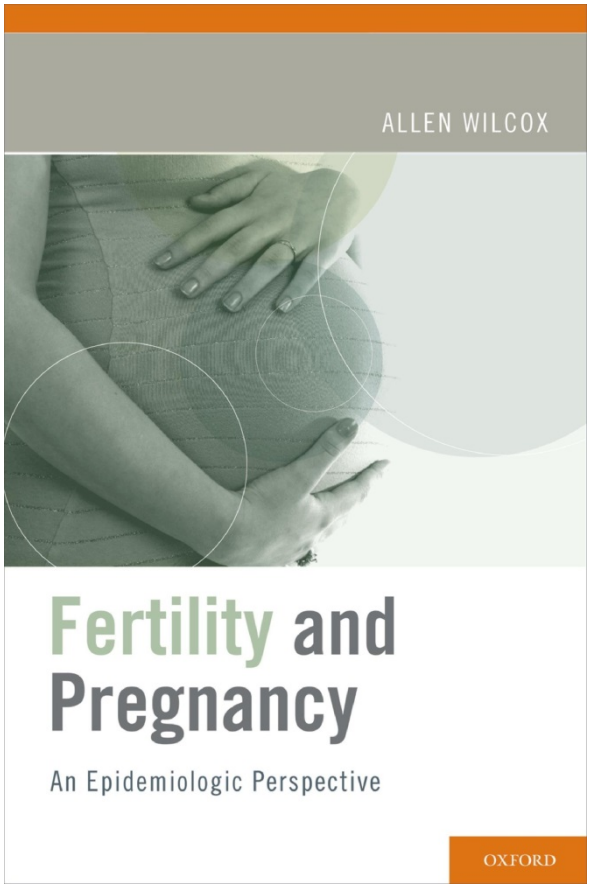
"The most challenging part of epidemiology…is to understand the reasons for human variability, including the reasons some people get a disease and others do not."[1]



[1] *Willcox (2010). Fertility and pregnancy: an epidemiologic perspective. Oxford Press.*

My goals for today:

- **Convince you** that testicular cancer is an important & time-critical area of research.
- **Detail and discuss** the peculiar epidemiology of this disease, and the aetiological clues that these patterns may provide.
- **Detail and discuss** the work that is underway within our research group.

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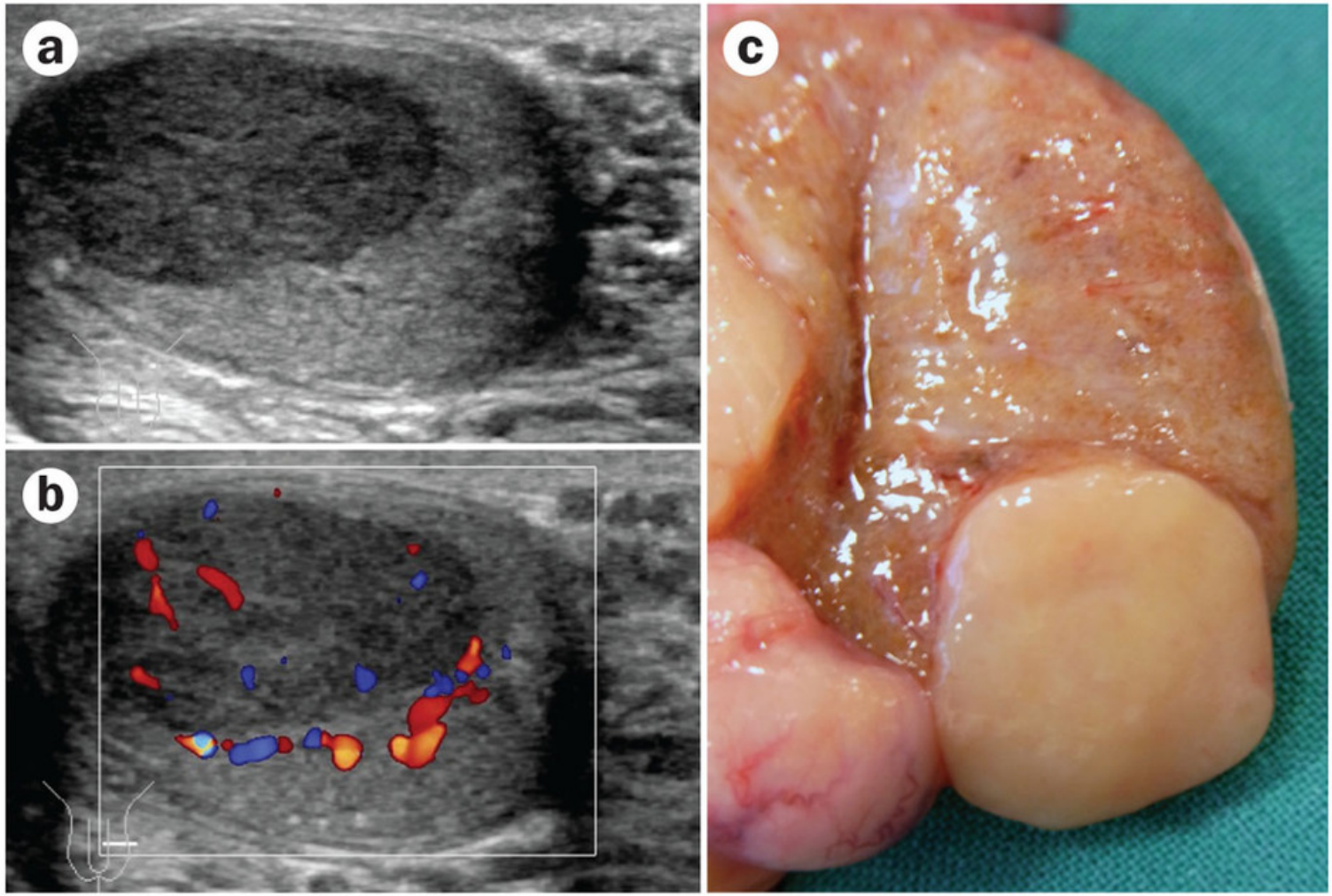

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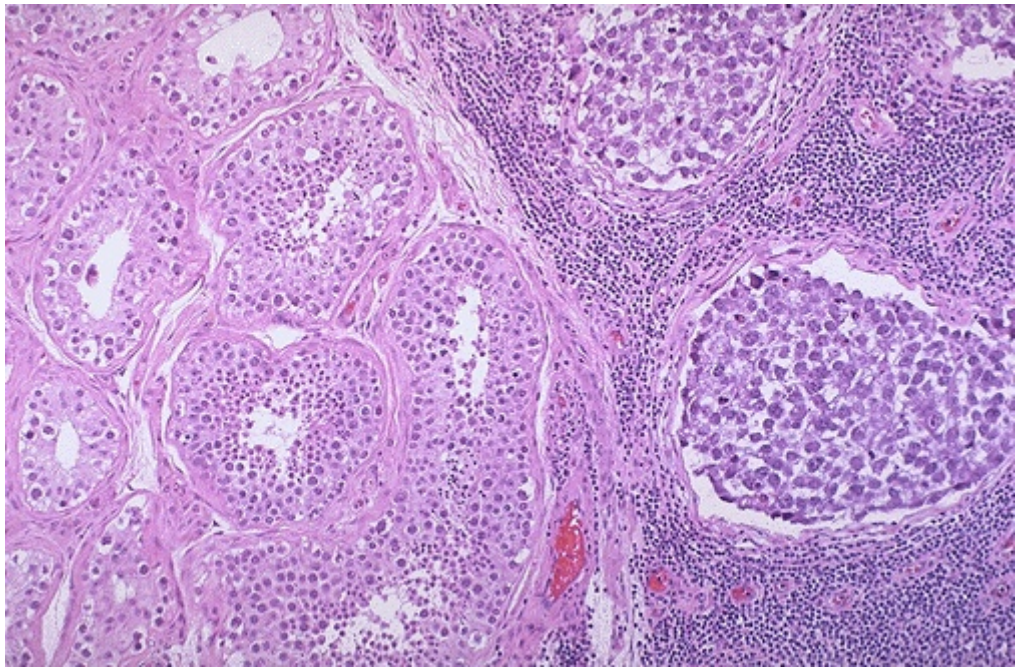
***Source**: Dieckmann, et al. (2013). Nature Reviews Urology, 10, p703-712.*

Normal germ cells



Tumour cell

***Source**: Male Genital Pathology Index, University of Utah (http://library.med.utah.edu/WebPath)*

Why is testicular cancer important?

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In a relative sense, testicular cancer (TC) is rare.

Cancer Among NZ Males, 2010

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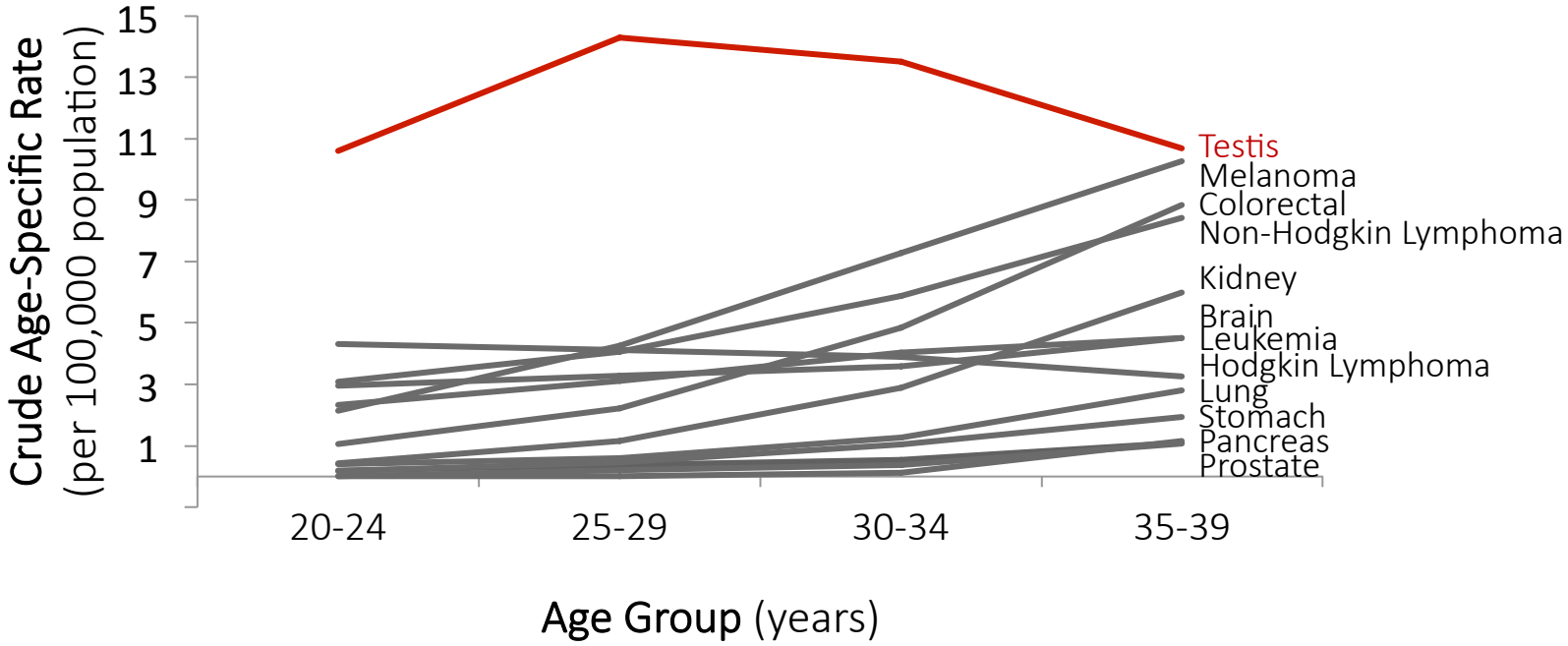
***Source**: MoH New Zealand Cancer Registry Historical Summary, 1948-2011*

However, testicular cancer is the most common cancer to afflict young men…

by a *considerable* margin.

Cancer Among U.S. Males, 2010



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Source: SEER Cancer Statistics Review, 1975-2011. National Cancer Institute.

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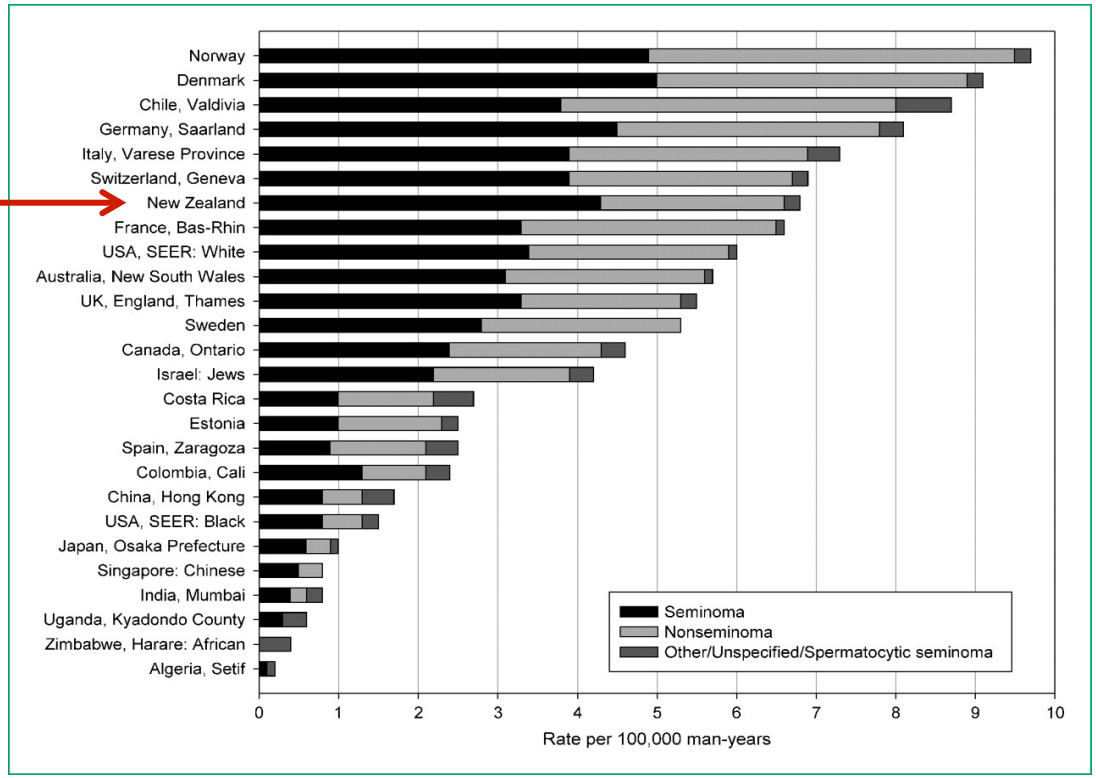
New Zealand has some of the highest rates of TC in the world.

Age-standardised incidence of TC (1998-2002)



[1]*Chia, et al. (2010). Cancer Epidemiol Biomarkers Prev, 19, p1151-1159.*

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Rates of TC are increasing steadily worldwide,[1] particularly among some populations.

No-one knows why.

[1] *Huyghe, et al. (2003). The Journal of Urology, 170, p5-11.*

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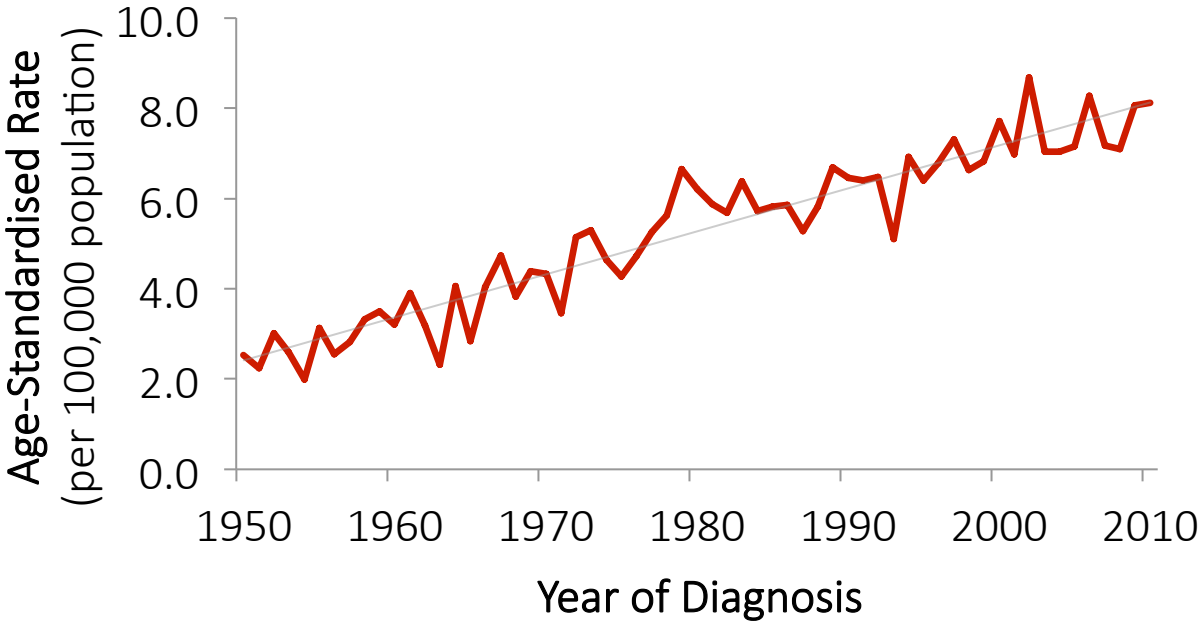
True to form, rates of TC in New Zealand are also increasing steadily over time:

Rates of TC in NZ, 1950-2010



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***Source**: MoH New Zealand Cancer Registry Historical Summary, 1948-2011*

What about the patients?

The Dirty 'P' Word…Prognosis

- Mercifully, survival among patients with TC is high.
  - We expect 90-100% will survive, for two main reasons:
    1. A tendency for this cancer to be detected early;
    2. The sophistication of modern treatment techniques.

The Dirty 'P' Word…Prognosis

- However, mortality isn't the only important outcome.
  - Around a *third* of TC survivors will be left infertile after treatment.
  - Increased risk of other sexual dysfunctions (like erectile dysfunction).
  - Because TC occurs mostly among young men, it casts a long shadow.

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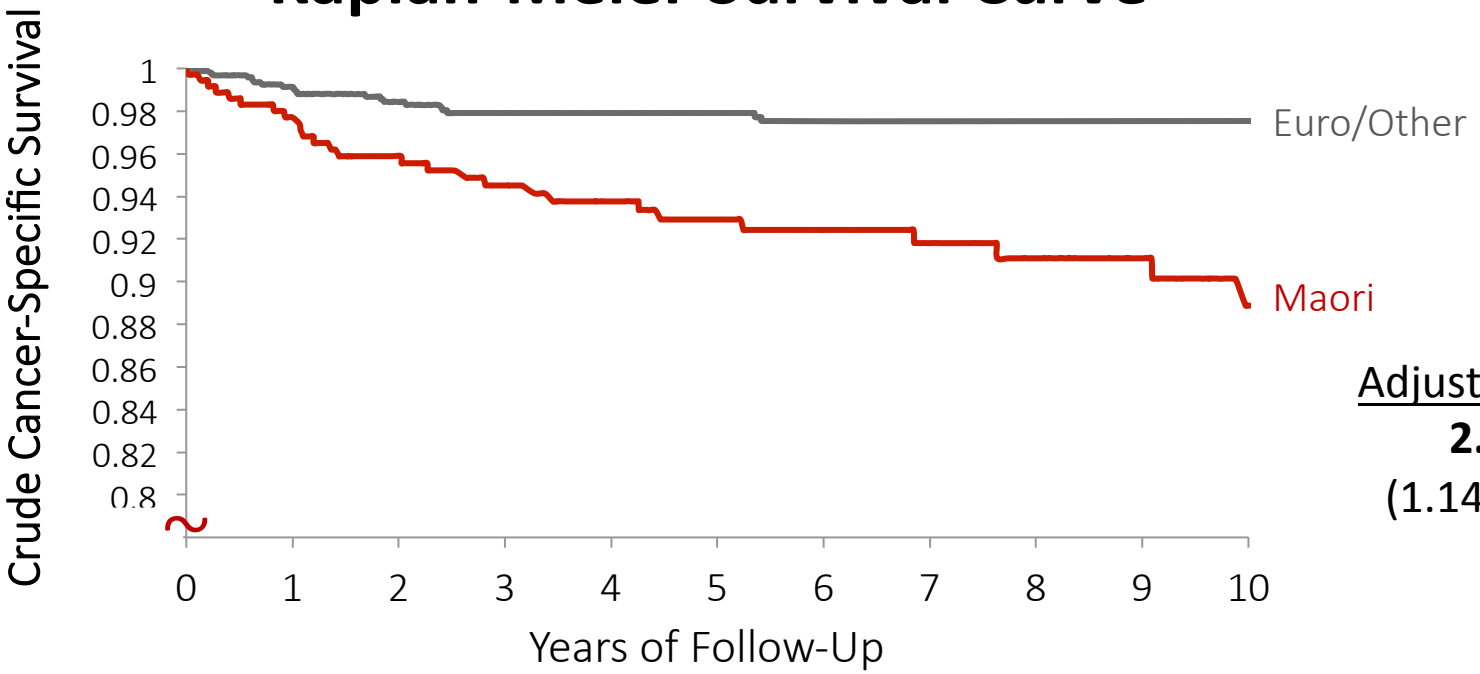
[1] *Brydøy, et al. (2005). J Nat Cancer Institute, 2005;97(21):1580-88.*

The Dirty 'P' Word…Prognosis

- Also, high overall survival could **mask survival inequalities**.
  - For example, Māori men are **more than twice as likely to die** of TC[1] than European/Other men:

[1] *Gurney, et al. (2015). Cancer Causes and Control, 26, p561-569.*

Kaplan-Meier Survival Curve



Adjusted HR:*
2.29
(1.14-4.59)

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[1] *Gurney, et al. (2015). Cancer Causes and Control, 26, p561-569.*
**Cancer-specific HR adjusted for age, stage, deprivation and rurality.*

What causes TC?

Unfortunately, the aetiology of TC remains obscure.

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Only a few ‘strong’ risk factors have been established:

- Age;
- Previous TC;
- Family history;
- ‘Cryptorchidism’.

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Aside from age, these known risk factors only account for a small number of TC cases.

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Because of this aetiological obscurity, TC is a heavily-researched area…

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…and as a result, there have been a myriad of other exposures associated (rightly or wrongly) with TC development:

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Month of birth
Ethnicity
PCBs
Cannabis
Testicular trauma
Fire fighting
Heavy metals
Childhood infections
Serum cholesterol
Aircraft maintenance
Agricultural work
Polychlorinated biphenyls
Hormone exposure
Retained placenta
SES
Nonionizing radiation
Pregnancy medications
Gestational hypertension
Parent occupation
Pre-eclampsia
Testicular temperature
EMF
Polyvinyl chloride
Maternal infections
Pesticides
Age at puberty
Diet
RH antibodies
Hypospadias
Subfertility
Marital status
Smoking
Androgen

Ethnicity

Curiouser and Curiouser

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Worldwide, the incidence of TC is (*by far*) the greatest among those ethnic groups who trace their ancestry to Northern Europe.[1]

[1] *McGlynn & Cook (2010). Chapter 2, Male Reproductive Cancers. Springer.*

In the U.S., White men are four-to-five times more likely to develop TC than Black men...[1]

[1] *McGlynn, et al. (2003). Cancer; 97, p63–70.*

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…and three-to four times more likely than Asian or Pacific Men.[1]

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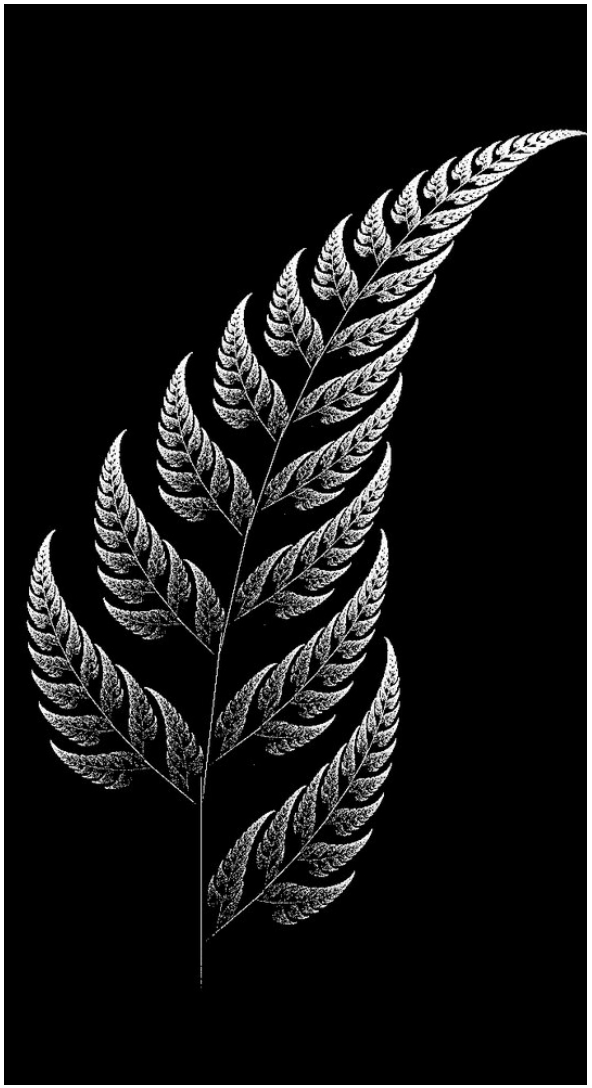
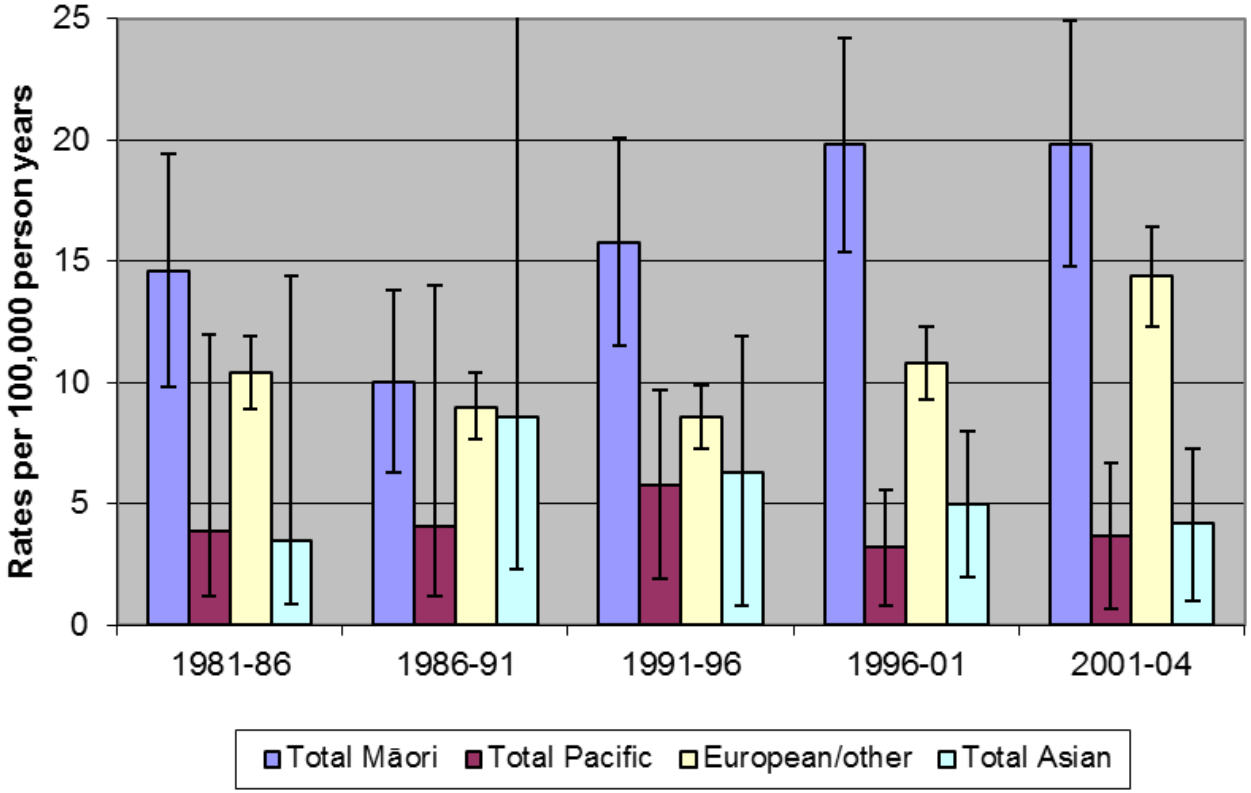
[1] *Chien, et al. (2014). Cancer; 120, p2728-2734.*

But in New Zealand, we've observed something very peculiar:



Incidence of TC in NZ by Ethnicity, 1981-2004



Source: Sarfati, et al. (2010). International Journal of Cancer, 128, p1683-1691.

In an updated study covering the years 2000-2011, Māori men were 80% more likely to develop TC than Euro/Other men.[1]

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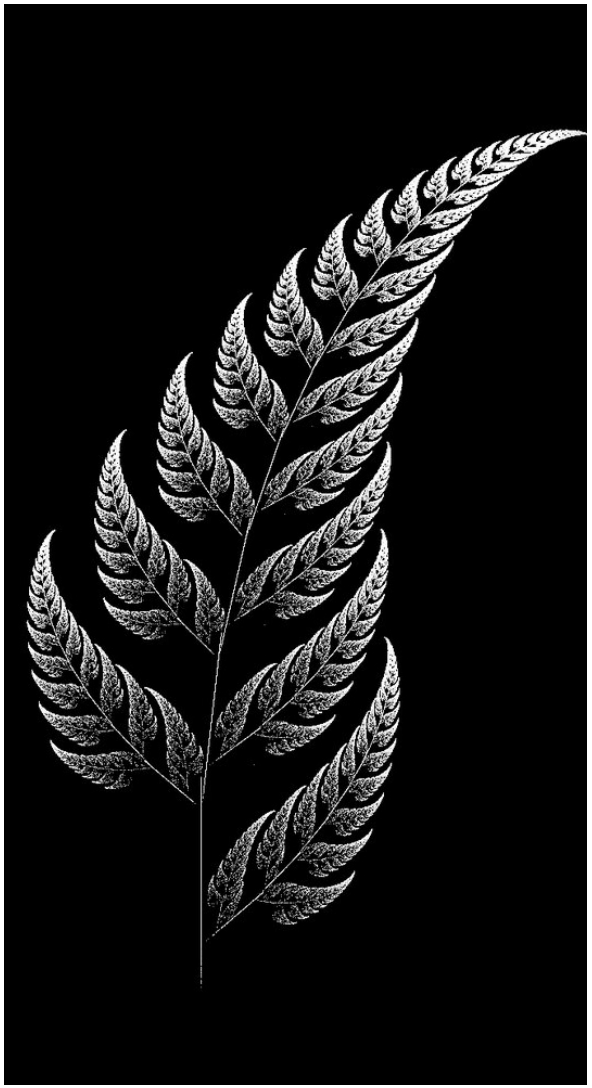
[1] *Gurney, et al. (2015). Cancer Causes and Control, 26, p561-569.*

Māori men were also three-times more likely than Pacific men to develop TC over this time period.

(Adjusted RR=3.13, 95% CI 2.28-4.29)



This is really weird.

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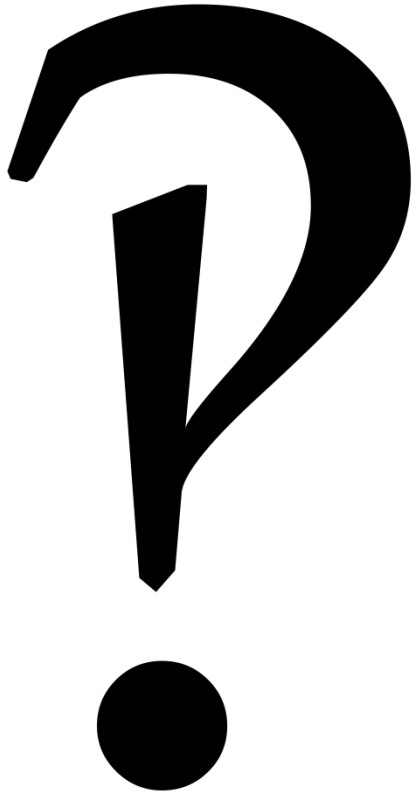
Curiouser…

The New Zealand context is the only (known) example where a non-White population experiences the greatest rates of TC.[1]



[1] *McGlynn & Cook (2010). Chapter 2, Male Reproductive Cancers. Springer.*

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…and Curiouser:

The low rates of TC found among Pacific New Zealanders is a rare example where disease incidence does not move in parallel between Māori and Pacific.

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"Given the lack of understanding of the aetiology of testicular cancer, the unusual patterns identified in the New Zealand context may provide some etiological clues for future novel research."[1]

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[1] *Sarfati, et al. (2010). International Journal of Cancer, 128, p1683-1691.*

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In other words, we have a unique opportunity in New Zealand to both explain an inequity *and* strengthen aetiological evidence.

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So that’s what we’re doing.

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Step 1:

The Cryptorchidism Study

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We know that, aside from age, cryptorchidism is the strongest known risk factor for TC.

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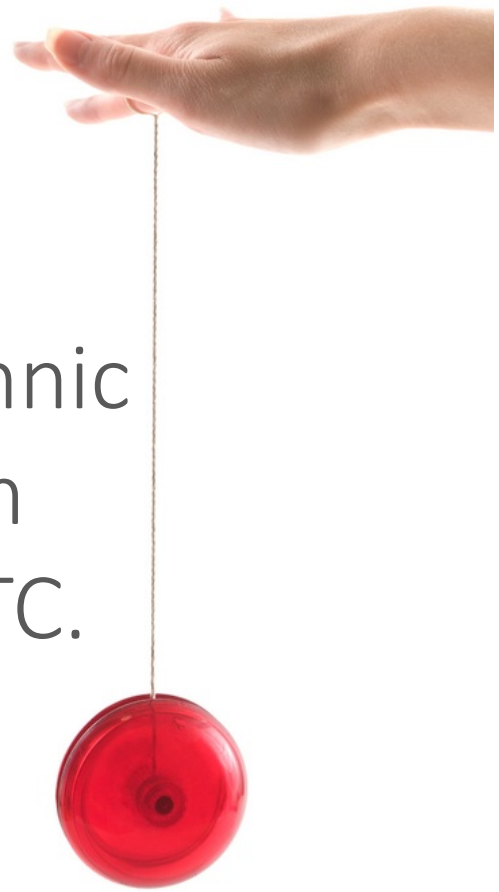
So, we decided to check whether ethnic patterns in rates of cryptorchidism mirror those that we observed for TC.



Why?

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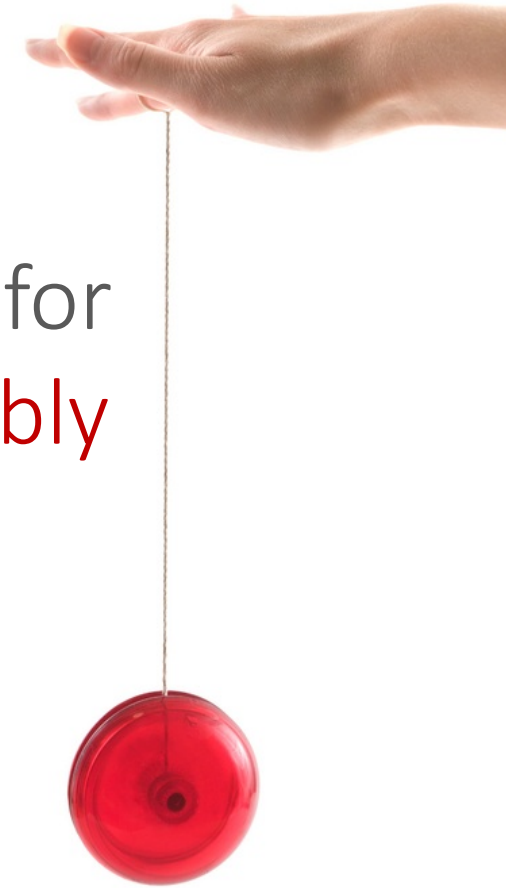
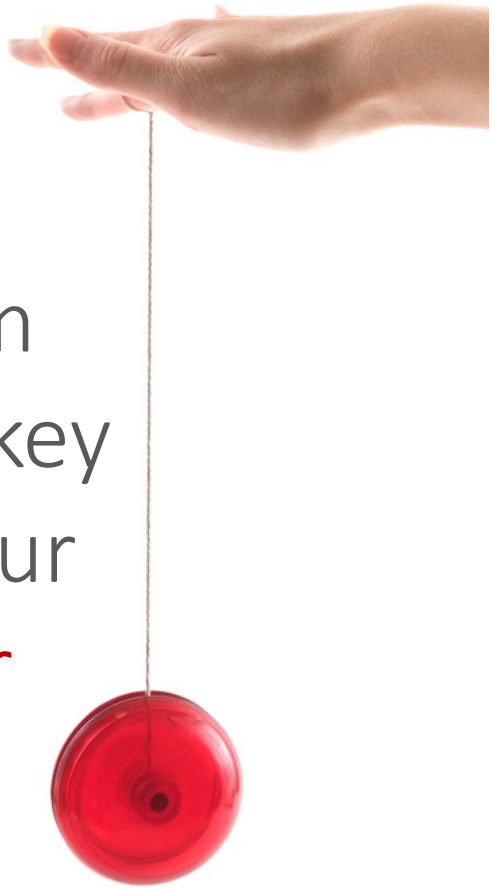
The primary exposures responsible for cryptorchidism development probably occur prenatally.

Maternal health
Gestational age
Hormone exposure
Size for gestational age
Low birth weight
Genetics
Maternal smoking?

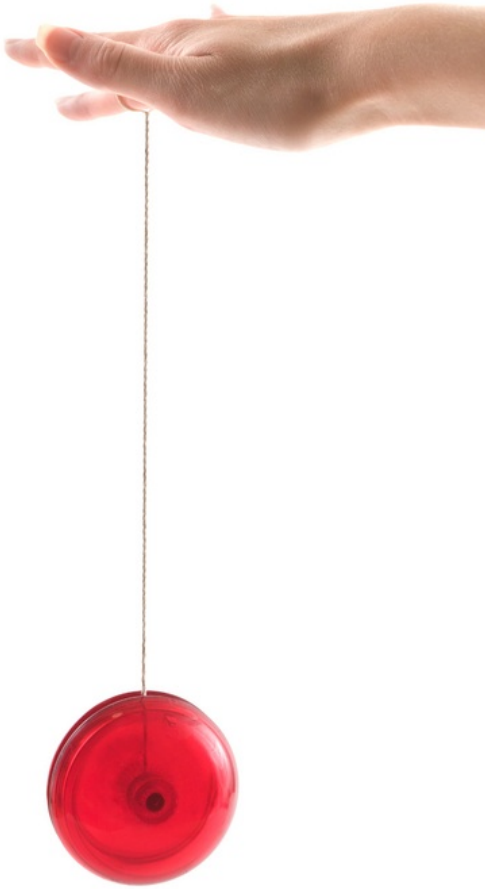


So…

If ethnic patterns of cryptorchidism reflect those found for TC, then the key exposures which lead to TC – and our ethnic inequality – probably occur prenatally too.



If this is true, we can focus our aetiological efforts on prenatal exposures.



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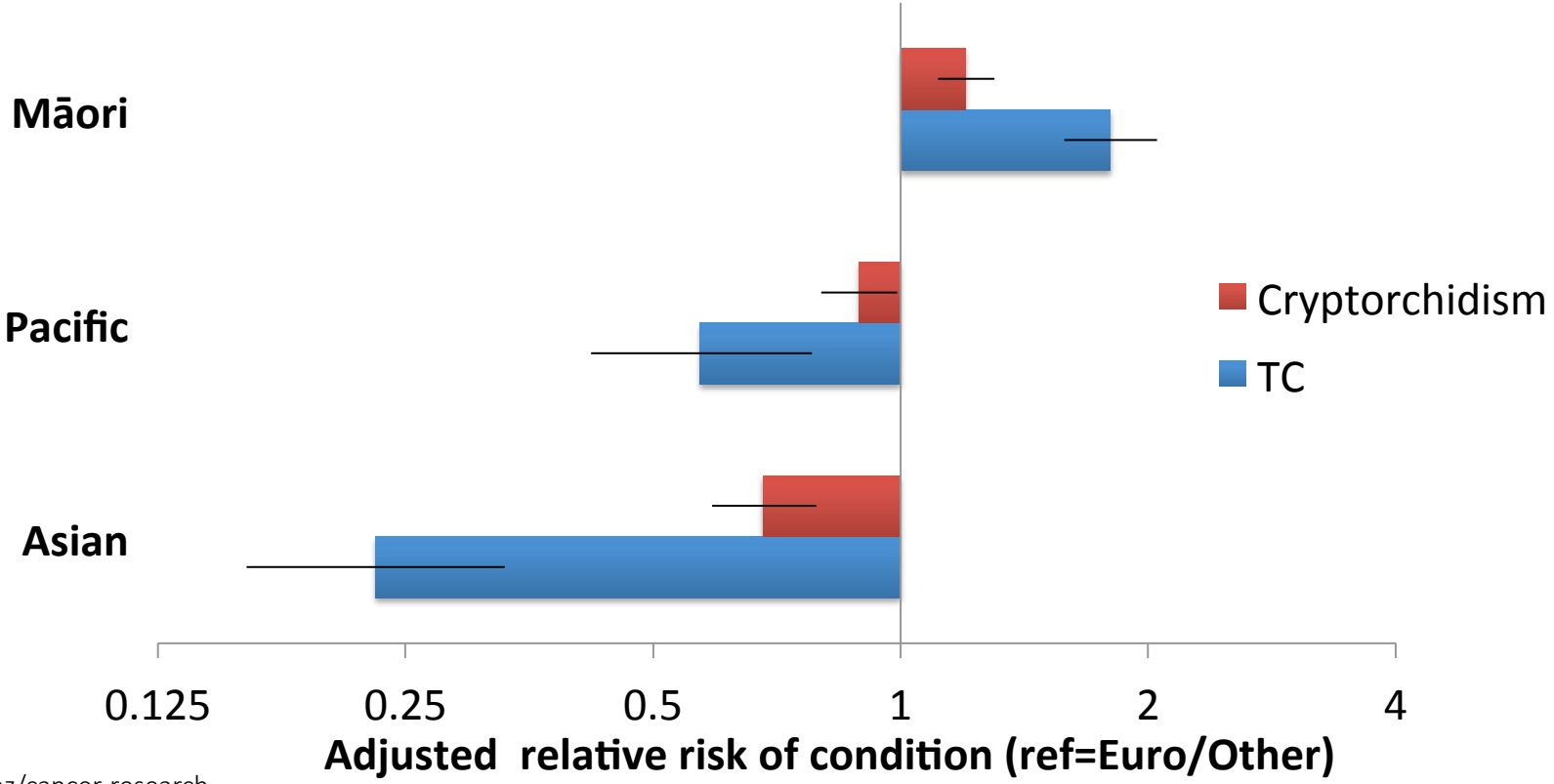
So we took a birth cohort of ~318,000 males born in NZ, and looked at the occurrence of orchidopexy-confirmed cryptorchidism.

Relative risk of TC and Cryptorchidism in NZ



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Source: *Gurney, et al. (2015). Andrology, Accepted and In Press.*

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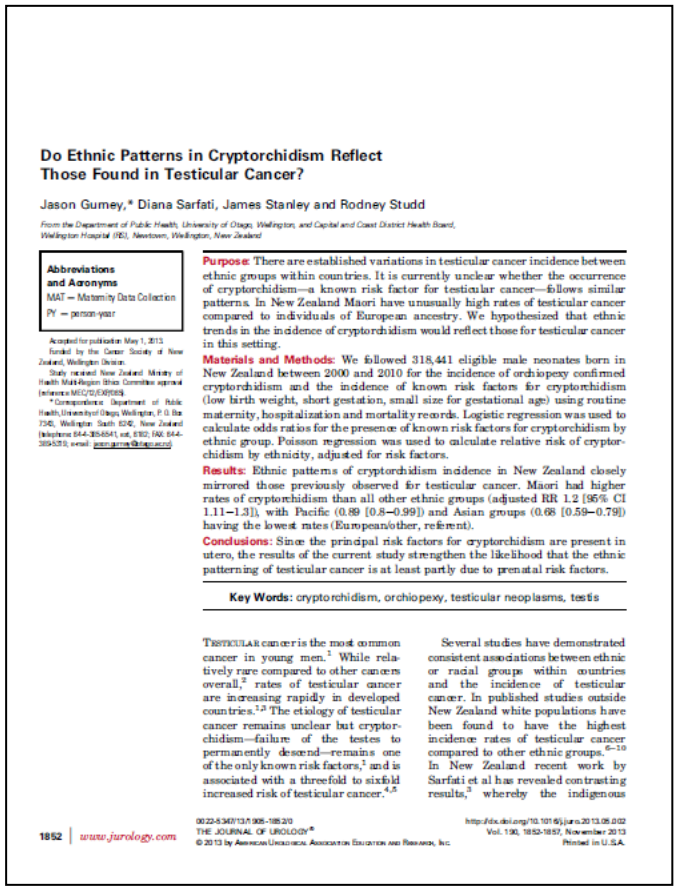
"Future research in this area should be focused on the genetic and environmental exposures that could disrupt normal testicular descent."[1]



Do Ethnic Patterns in Cryptorchidism Reflect Those Found in Testicular Cancer?

Jason Gurney,* Diana Sarfati, James Stanley and Rodney Studd

From the Department of Public Health, University of Otago, Wellington, and Capital and Coast District Health Board, Wellington Hospital (RS), Newtown, Wellington, New Zealand

Abbreviations and Acronyms
MAT = Maternity Data Collection
PY = person-year

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Funded by the Cancer Society of New Zealand, Wellington Division.
Study received New Zealand Ministry of Health Multi-Region Ethics Committee approval (reference MEC/12/EXP/005).
* Correspondence: Department of Public Health, University of Otago, Wellington, P. O. Box 7343, Wellington South 6242, New Zealand (telephone 644-385-6541, ext. 8182; FAX 644-385-6373; e-mail: jason.gurney@otago.ac.nz).

Purpose: There are established variations in testicular cancer incidence between ethnic groups within countries. It is currently unclear whether the occurrence of cryptorchidism—a known risk factor for testicular cancer—follows similar patterns. In New Zealand Maori have unusually high rates of testicular cancer compared to individuals of European ancestry. We hypothesized that ethnic trends in the incidence of cryptorchidism would reflect those for testicular cancer in this setting.

Materials and Methods: We followed 318,441 eligible male neonates born in New Zealand between 2000 and 2010 for the incidence of orchiopexy confirmed cryptorchidism and the incidence of known risk factors for cryptorchidism (low birth weight, short gestation, small size for gestational age) using routine maternity, hospitalization and mortality records. Logistic regression was used to calculate odds ratios for the presence of known risk factors for cryptorchidism by ethnic group. Poisson regression was used to calculate relative risk of cryptorchidism by ethnicity, adjusted for risk factors.

Results: Ethnic patterns of cryptorchidism incidence in New Zealand closely mirrored those previously observed for testicular cancer. Maori had higher rates of cryptorchidism than all other ethnic groups (adjusted RR 1.2 [95% CI 1.11–1.31]), with Pacific (0.89 [0.8–0.99]) and Asian groups (0.68 [0.59–0.79]) having the lowest rates (European/other, referent).

Conclusions: Since the principal risk factors for cryptorchidism are present in utero, the results of the current study strengthen the likelihood that the ethnic patterning of testicular cancer is at least partly due to prenatal risk factors.

Key Words: cryptorchidism, orchiopexy, testicular neoplasms, testis

TESTICULAR cancer is the most common cancer in young men.[1] While relatively rare compared to other cancers overall,[2] rates of testicular cancer are increasing rapidly in developed countries.[1,2] The etiology of testicular cancer remains unclear but cryptorchidism—failure of the testes to permanently descend—remains one of the only known risk factors,[3] and is associated with a threefold to sixfold increased risk of testicular cancer.[4,5]

Several studies have demonstrated consistent associations between ethnic or racial groups within countries and the incidence of testicular cancer. In published studies outside New Zealand white populations have been found to have the highest incidence rates of testicular cancer compared to other ethnic groups.[6–10] In New Zealand recent work by Sarfati et al has revealed contrasting results,[3] whereby the indigenous

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[1] *Gurney, et al. (2013). The Journal of Urology, 190, p1852-1857.*

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Step 2:

Testicular Dysgenesis Syndrome

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Testicular cancer is thought by many researchers to be one part of a single syndrome called Testicular Dysgenesis Syndrome (TDS).

This syndrome asserts that TC, cryptorchidism, ‘hypospadias’, and poor semen quality largely share the same risk factors.

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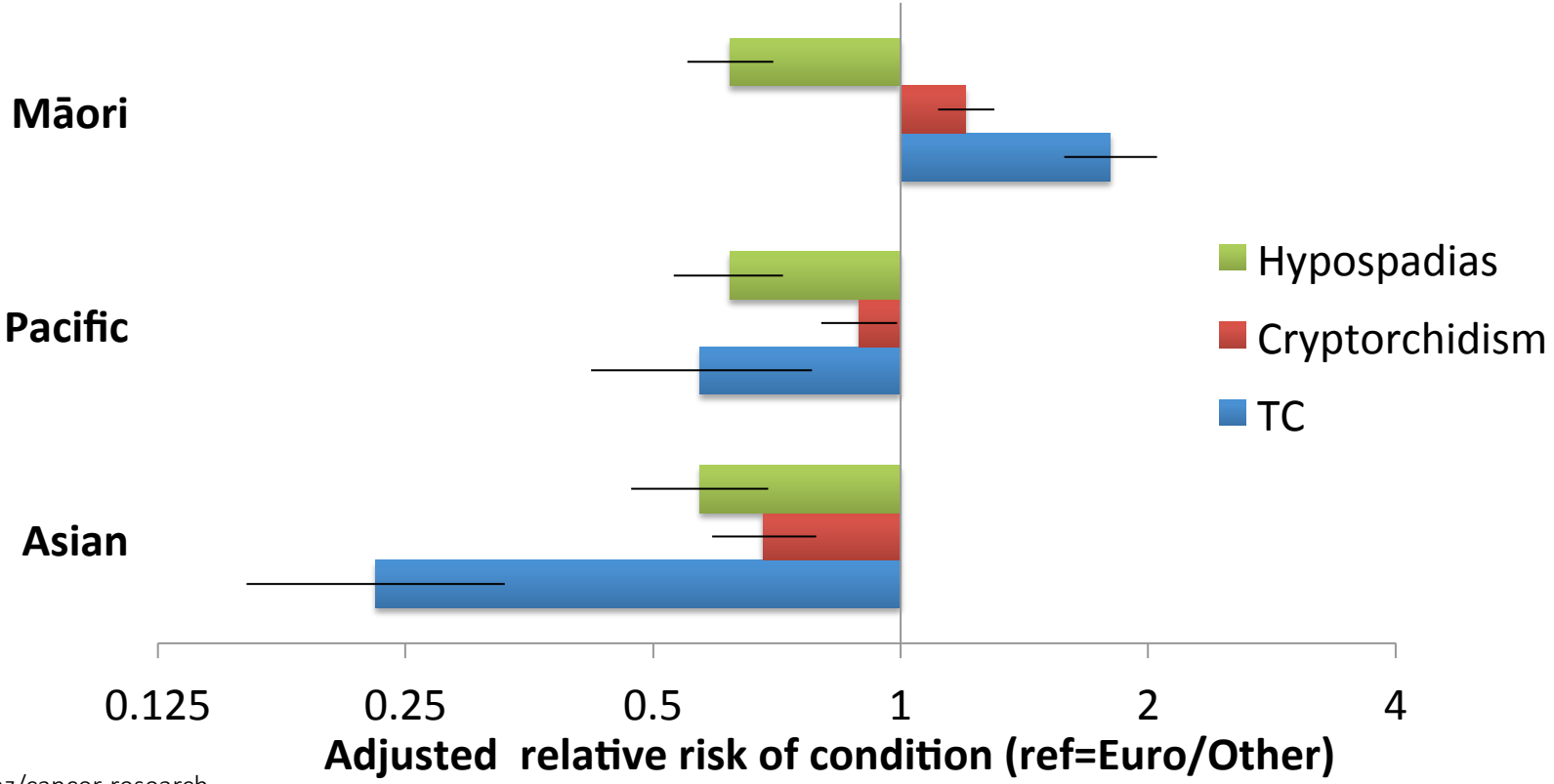
It’s an appealing concept.

If this were true, then it follows that we should observe the same unusual ethnic patterns for all of these conditions.

Except we don’t.

Relative risk of TC, Cryptorchidism and Hypospadias



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Source: Gurney, et al. (2015). Andrology, Accepted and In Press.

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"Our observations suggest…that the exposures that drive the development of hypospadias differ to those that that drive the development of cryptorchidism and/or testicular cancer."[1]

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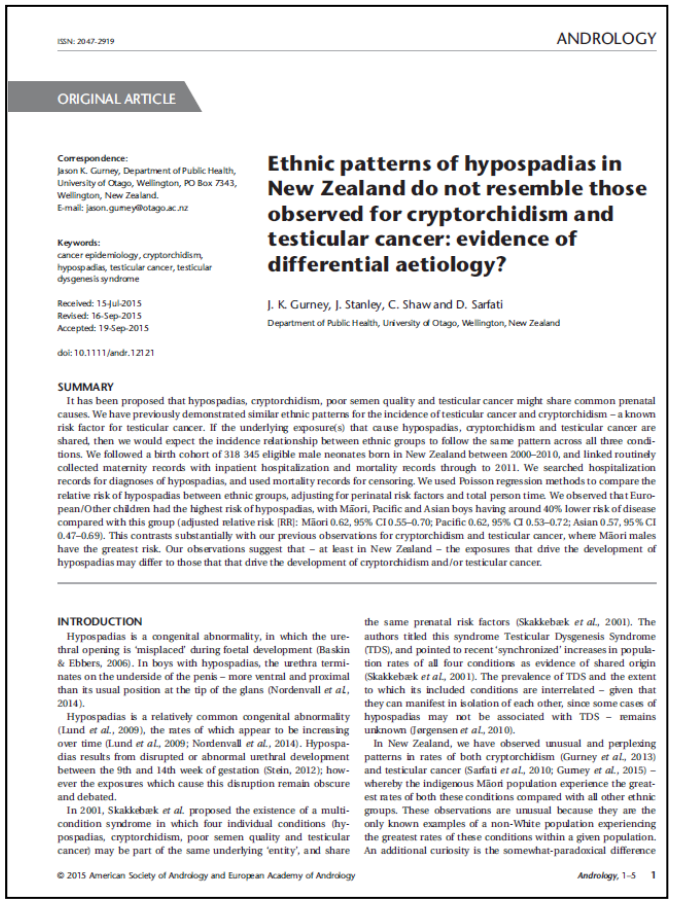

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ORIGINAL ARTICLE

Correspondence:
Jason K. Gurney, Department of Public Health, University of Otago, Wellington, PO Box 7343, Wellington, New Zealand.
E-mail: jason.gurney@otago.ac.nz

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Ethnic patterns of hypospadias in New Zealand do not resemble those observed for cryptorchidism and testicular cancer: evidence of differential aetiology?

J. K. Gurney, J. Stanley, C. Shaw and D. Sarfati
Department of Public Health, University of Otago, Wellington, New Zealand

SUMMARY

It has been proposed that hypospadias, cryptorchidism, poor semen quality and testicular cancer might share common prenatal causes. We have previously demonstrated similar ethnic patterns for the incidence of testicular cancer and cryptorchidism – a known risk factor for testicular cancer. If the underlying exposure(s) that cause hypospadias, cryptorchidism and testicular cancer are shared, then we would expect the incidence relationship between ethnic groups to follow the same pattern across all three conditions. We followed a birth cohort of 318 345 eligible male neonates born in New Zealand between 2000–2010, and linked routinely collected maternity records with inpatient hospitalization and mortality records through to 2011. We searched hospitalization records for diagnoses of hypospadias, and used mortality records for censoring. We used Poisson regression methods to compare the relative risk of hypospadias between ethnic groups, adjusting for perinatal risk factors and total person time. We observed that European/Other children had the highest risk of hypospadias, with Māori, Pacific and Asian boys having around 40% lower risk of disease compared with this group (adjusted relative risk [RR]: Māori 0.62, 95% CI 0.55–0.70; Pacific 0.62, 95% CI 0.53–0.72; Asian 0.57, 95% CI 0.47–0.69). This contrasts substantially with our previous observations for cryptorchidism and testicular cancer, where Māori males have the greatest risk. Our observations suggest that – at least in New Zealand – the exposures that drive the development of hypospadias may differ to those that that drive the development of cryptorchidism and/or testicular cancer.

INTRODUCTION

Hypospadias is a congenital abnormality, in which the urethral opening is 'misplaced' during foetal development (Baskin & Ebbers, 2006). In boys with hypospadias, the urethra terminates on the underside of the penis – more ventral and proximal than its usual position at the tip of the glans (Nordenvall *et al.*, 2014).

Hypospadias is a relatively common congenital abnormality (Lund *et al.*, 2009), the rates of which appear to be increasing over time (Lund *et al.*, 2009; Nordenvall *et al.*, 2014). Hypospadias results from disrupted or abnormal urethral development between the 9th and 14th week of gestation (Stein, 2012); however the exposures which cause this disruption remain obscure and debated.

In 2001, Skakkebæk *et al.* proposed the existence of a multi-condition syndrome in which four individual conditions (hypospadias, cryptorchidism, poor semen quality and testicular cancer) may be part of the same underlying 'entity', and share the same prenatal risk factors (Skakkebæk *et al.*, 2001). The authors titled this syndrome Testicular Dysgenesis Syndrome (TDS), and pointed to recent 'synchronized' increases in population rates of all four conditions as evidence of shared origin (Skakkebæk *et al.*, 2001). The prevalence of TDS and the extent to which its included conditions are interrelated – given that they can manifest in isolation of each other, since some cases of hypospadias may not be associated with TDS – remains unknown (Jørgensen *et al.*, 2010).

In New Zealand, we have observed unusual and perplexing patterns in rates of both cryptorchidism (Gurney *et al.*, 2013) and testicular cancer (Sarfati *et al.*, 2010; Gurney *et al.*, 2015) – whereby the indigenous Māori population experience the greatest rates of both these conditions compared with all other ethnic groups. These observations are unusual because they are the only known examples of a non-White population experiencing the greatest rates of these conditions within a given population. An additional curiosity is the somewhat-paradoxical difference

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[1] *Gurney, et al. (2015). Andrology, Accepted and In Press.*

So what’s next?

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To investigate more about the aetiology of testicular cancer, we plan to conduct two separate *case-control* studies:

a cryptorchidism CCS; and

a testicular cancer CCS.

Both studies will focus on trying to understand why Māori have the greatest rates of both conditions in New Zealand.

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Our burning questions:

- Why are Māori men the only non-White ethnic group to experience the highest rates of these conditions in a given population?
- Polynesian Paradox: Why are Māori males so much more likely to develop these conditions than Pacific males?
- What are we missing?

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