Testicular cancer in New Zealand: A mystery to be solved

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Our questions for today:

• Why is testicular cancer **important**?

• What **causes** testicular cancer?

• Why might New Zealand have an **important role to play** in understanding this disease?
“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.”

What is TC?

• Testicular cancer is, well, cancer of the testis.
  – Almost all (95%)\(^1\) TC’s begin within germ cells – the cells that give rise to sperm.

Normal germ cells

Tumour cell

Source: Male Genital Pathology Index, University of Utah (http://library.med.utah.edu/WebPath)
Why is testicular cancer important?
In a relative sense, testicular cancer (TC) is rare.
Cancer Among NZ Males, 2010

Selected Sites

Age-Standardised Rate (per 100,000 population)

Prostate: 99
Colorectal: 49
Melanoma: 43
Lung: 34
Kidney: 15
Leukaemia: 13
Bladder: 13
Pancreas: 9
Testis: 8
Stomach: 8
Brain: 7
Liver: 6
Myeloma: 6
Thyroid: 3
Hodgkin Lymphoma: 2

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

Crude Age-Specific Rate (per 100,000 population)

Age Group (years)

Testis
Melanoma
Colorectal
Non-Hodgkin Lymphoma
Kidney
Brain
Leukemia
Hodgkin Lymphoma
Lung
Stomach
Pancreas
Prostate

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

Rates of TC are increasing steadily worldwide, particularly among some populations. No-one knows why.

True to form, rates of TC in New Zealand are also increasing steadily over time:
Rates of TC in NZ, 1950-2010

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

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:

Adjusted HR: *2.29 (1.14-4.59)

*Cancer-specific HR adjusted for age, stage, deprivation and rurality.

What causes TC?
Unfortunately, the aetiology of TC remains obscure.
Only a few ‘strong’ risk factors have been established:

- Age;
- Previous TC;
- Family history;
- ‘Cryptorchidism’.
Aside from age, these known risk factors only account for a small number of TC cases.
Because of this aetiological obscurity, TC is a heavily-researched area...
...and as a result, there have been a myriad of other exposures associated (rightly or wrongly) with TC development:
Ethnicity
Curiouser and Curiouser
Worldwide, the incidence of TC is (by far) the greatest among those ethnic groups who trace their ancestry to Northern Europe.¹

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

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

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

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

(Age-adjusted RR=1.80, 95% CI 1.58-2.05)

Māori men were also three-times more likely than Pacific men to develop TC over this time period. (Age-adjusted RR=3.13, 95% CI 2.28-4.29)
This is really weird.
Curiouser...
The New Zealand context is the only (known) example where a non-White population experiences the greatest rates of TC.¹

...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.
“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.”

In other words, we have a unique opportunity in New Zealand to both explain an inequity and strengthen aetiological evidence.
So that’s what we’re doing.
Testicular Cancer in New Zealand (TCNZ) Study
**The TCNZ Study**

- **Case-control study** design - ~400 TC cases, 400 non-TC controls (150 Māori in each).

- Collecting **environmental** exposure data via interview, and **genetic** exposure data via saliva sample.

- Also interviewing **mothers of cases/controls**, to look at exposures during pregnancy and early-life.
Our burning questions:

– Why do Māori men suffer the highest rates of testicular cancer in New Zealand? What is driving this disparity?

– What might we learn about the factors that cause testicular cancer in general by explaining this disparity?
We aim to start pilot data collection in 2018.
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Life.
(Not to scale)

Pre-Natal Exposures
- Birth weight
- Maternal smoking
- Cryptorchidism
- Gestational age

Post-Natal Exposures
- Smoking
- Occupation
- Cannabis
- Age at puberty

Genetic Exposures + Gene:Environment Interactions...
(...+Environment:Environment Interactions?)
Relative risk of TC and Cryptorchidism in NZ

Māori

Pacific

Asian

Adjusted relative risk of condition (ref=Euro/Other)

Source: Gurney, et al. (2015). Andrology, Accepted and In Press.
“Future research in this area should be focused on the genetic and environmental exposures that could disrupt normal testicular descent.”

Relative risk of TC, Cryptorchidism and Hypospadias

Adjusted relative risk of condition (ref=Euro/Other)

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

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