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# Oral cancer risk factors in New Zealand

Missing data on body mass index in a breast cancer register: how is it associated with patient characteristics and clinical outcomes?

**Body mass index (BMI):  
association with  
clinicopathological  
factors and outcome  
of women with newly  
diagnosed breast cancer  
in New Zealand**



**Learning from the 'Muslim ban':  
implications of the Trump presidency  
for international public health**

**PGY2 attachments in  
general practice—a New  
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**Can we help  
prevent mouth  
cancer?**

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## Patient response to use of tyrosine kinase inhibitors in lung cancer: a retrospective audit during funding changes

Anne Fraser

Therapies that target communication to cancer cells can be used to treat some lung cancer. This paper describes the clinical setting where targeted therapies work best for patients with a mutation driving their lung cancer, the response rates for patients and experience of side effects.

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## Missing data on body mass index in a breast cancer register: how is it associated with patient characteristics and clinical outcomes?

Sandar Tin Tin, J Mark Elwood, Ross Lawrenson, Ian Campbell

Patient's body mass index, which is calculated as weight/height<sup>2</sup>, can influence the outcomes of breast cancer. We assessed the completeness of data on patient height and weight in the Waikato Breast Cancer Register covering the period between January 2000 and June 2014. We found that height was not recorded on one in four patients and weight not recorded on one in six patients, and importantly the data was not missing at random. To be able to evaluate the associations between body mass index and breast cancer outcomes in New Zealand, patient height and weight should be recorded in hospital and computerised data systems.

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## Oral cancer risk factors in New Zealand

Muhammed Yakin, Ratu Osea Gavidu, Brian Cox, Alison Rich

Oral cancer is a significant health issue with high morbidity and mortality rates. With late diagnosis, approximately half of the affected patients die of the disease within five years. Certain factors, particularly alcohol and tobacco consumption, place individuals at a higher risk of getting oral cancer. In New Zealand, four out of five individuals consume alcohol and approximately two out of five use tobacco, which places them at higher risk of developing oral cancer. We have provided an overview of these and other oral cancer risk factors and their prevalence in New Zealand. We hope that this will further encourage doctors and dentists to provide regular advice regarding tobacco cessation and judicious alcohol use.

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## Individualised follow-up booklets improve recall and satisfaction for cancer patients

Hoani MacFater, Wiremu MacFater, Andrew Hill, Marianne Lill

This study investigated the use of providing individualised follow-up information to cancer patients in the form of a structured booklet containing their results, treatment summary and follow-up plan as well as general information. Patients were interviewed by phone to assess their recall of what was needed for their follow up and how satisfied they were with their follow-up plan. Patients who received a personalised booklet as part of their follow up had greater recall of, and greater satisfaction with their follow-up plans compared to an earlier group of patients who did not receive a booklet. This supports the recommendation that patients be provided with personalised written information as part of their follow up.

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## Body mass index (BMI): association with clinicopathological factors and outcome of women with newly diagnosed breast cancer in New Zealand

Bridget Robinson, Margaret Currie, Elisabeth Phillips, Gabi Dachs, Matthew Strother, Helen Morrin, Val Davey, Chris Frampton

We studied women who had been diagnosed with breast cancer and had been recorded on the four Breast Cancer Registers in Auckland, Waikato, Wellington and Christchurch. Just as in the New Zealand population, one-third of these women with breast cancer were overweight and a further one-third were obese. Overweight and obese women tended to have their cancer found on cancer screening, rather than from checking symptoms, and they tended to be larger cancers of higher grade. As has been found overseas, the younger women with the greatest degree of obesity tended to have a poorer outcome when treated with chemotherapy. This argues for ongoing cooperating of women with screening programmes, and aiming to reduce weight and increase physical activity, both in general and after diagnosis of breast cancer.

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## Reducing the polyp burden in serrated polyposis by serial colonoscopy: the impact of nationally coordinated community surveillance

Susan Parry, Randall W Burt, Aung Ko Win, Ye Kyaw Aung, Sonja Woodall, Julie Arnold, Mark Clendenning, Daniel D Buchanan, Timothy J Price, Christophe Rosty, Joanne P Young

Serrated polyposis is associated with an increased risk of bowel cancer, and is now being increasingly recognised. Current recommendations suggest that patients with serrated polyposis undergo surveillance in specialist tertiary centres. However, in the real world, patients undergo surveillance in a variety of community settings with variable levels of medical expertise. In this long-term study we have shown that it is possible to safely manage patient surveillance in the community using a tertiary centre monitoring system providing feedback regarding surveillance intervals and prophylactic surgery.

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# Can we help prevent mouth cancer?

Leslie Snape, Derek W Goodisson

**D**iagnosis and management of patients with oral cancer has developed significantly in the last 30 years with the introduction of more sensitive imaging, refined histological techniques, appropriate staging, improved surgical reconstruction and targeted radiotherapy. However, despite these advances, this disease causes considerable morbidity with often severely compromised function and possible disfigurement. Although head and neck cancer, excluding lymphoma, skin cancer and melanoma, represents only 2.5% of all cancers, it carries with it significant social and economic implications.

Oral squamous cell carcinoma (OSCC) affects any site from the lips throughout the mouth, including buccal mucosa, tongue, floor of mouth, gingiva and palate, posteriorly to the junction with the oropharynx. During 2014, excluding lips, there were 225 new cases of mouth cancer reported to the New Zealand Cancer Registry, the majority of these affecting the tongue.<sup>1</sup> Oral SCC presents largely in patients over 45 years of age, however, there has been a steady increase in the incidence of head and neck cancer in younger patients, most likely attributable to exposure to human papilloma virus (HPV).<sup>2</sup>

Management for patients with a diagnosis of oral cancer will usually involve surgery, and depending on staging may also include postoperative adjunctive external beam radiotherapy to the lower face and neck. Head and neck cancer in New Zealand, as with other cancer types, is managed through multidisciplinary meetings (MDM) ensuring standardisation of care and timeliness of delivery, audited through the Ministry of Health (MoH).<sup>3</sup>

Function may well be compromised after treatment, with altered speech, difficulties with mastication, swallowing, dry mouth, altered sensation and in advanced cases facial disfigurement. Post-treatment surveillance will usually continue for five years,

with recurrence of disease and survival depending on initial stage at diagnosis.

Numerous studies have addressed quality-of-life in these patients, illustrating the burden of not only the diagnosis but the ongoing difficulties these patients may face on a day-to-day basis.<sup>4,5</sup> These studies showed that because of the nature of their disease, patients are negatively affected by the different types of surgical treatment for oral and oropharyngeal cancers, with both early and late interrelated effects, and by the side effects of adjuvant therapy. In addition to the difficulty with physical aspects of their rehabilitation after surgery and radiotherapy, these patients often have considerable psychosocial issues.

The paper by Yakin et al<sup>6</sup> from the Dunedin Oral Pathology Department provides an excellent review of the risk factors for the development of oral cancer in the New Zealand population and should remind clinicians of the importance of advice on smoking cessation and alcohol intake, with early referral and diagnosis, which can help reduce the impact on quality-of-life for these patients. Dental practitioners in particular have a very important role of vigilance in patients attending for examination and treatment, but medical practitioners should also be alert to the patient who presents with “I’ve got an ulcer in my mouth” or a lump.

It is now accepted that as with cervical cancer, HPV plays a significant role in head and neck cancer. In New Zealand, 75% of oropharyngeal cancers are HPV related.<sup>7</sup> PHARMAC has recently recognised this in subsidising vaccination with Gardasil® 9 for both teenage boys and girls, and this editorial strongly supports vaccination against HPV. HPV-associated head and neck cancer carries a much better prognosis than non-HPV.<sup>8</sup>

Clearly the public health message needs to address the impact of smoking and alcohol, with the finding that smoking increases the risk of oral cancer by a factor of four

to 20 times, and alcohol drinkers may have a two-and-a-half to five times risk. But the Yakin et al paper highlights another concern with the increasing availability in New Zealand and use of water-pipe smoking (hookah, shisha, nargileh), which is popular among Middle Eastern communities. This method of tobacco use exposes the aerodigestive tract to substantially greater amounts of carcinogens than cigarettes.

Although the number of cases presenting with OSCC are relatively small compared to such cancers as breast, colon or prostate, early diagnosis of oral cancer, as with most cancers, results in improved outcomes.

Mouth ulcers not healing within 3–4 weeks may need to be biopsied, and early referral for specialist review indicated. Referrals indicating ‘High Suspicion of Cancer’ (HSC) are red flagged, and according to MoH guidelines should be seen within two weeks.<sup>3</sup>

In the future, the management of oral SCC may follow the same targeted therapy path similar to other cancer types (for example breast and melanoma).<sup>8</sup> For now though, it remains largely a preventable disease which, through education and vaccination, will hopefully see a progressive decline in incidence not only in New Zealand, but globally.

**Competing interests:**

Nil.

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# In absentia: describing the toll of war on health in Syria

Vanessa Cramond, Matthew Reid

**I**n our line of work we rely on numbers. The number of patients treated in the clinics, the number of children with pneumonia, or diarrhoea or severe malnutrition, the number of patients admitted to the hospital, the number of patients undergoing emergency surgery, the number of babies born, the number of children vaccinated, the number of people counselled.

The numbers guide us to where the needs are, what is making people sick, how difficult it might be to reach health care by how late and sick the patients are when they present to hospital, and the number of deaths and where and when they happen. These are all ways of measuring how the health system is performing. They paint a picture from which we can describe, interpret and then plan how best to reach a population's health needs. We can adjust medical interventions in order to treat more people, to reduce disease burden and avert death. The central tenant is to provide health care, alleviate suffering and provide comfort to people. Not just those patients directly in front of us, but everyone around them. Numbers are important; without them we cannot effectively do our job.

In New Zealand we are fortunate that we have the information we need to allocate resources effectively. In war-torn Syria, patients are besieged and in inaccessible areas. True numbers are unknown, those that we do see paint a picture so bleak, the size and scale of the emergency health response seems unimaginable.

For six long years, war has waged across Syria, resulting in an unprecedented 4.8 million people becoming refugees.<sup>1</sup> The responsibility to care for this refugee population falls largely to Syria's neighbours.<sup>1</sup> Inside Syria, the United Nations High Commission for Refugees have some overwhelming numbers. They report that 13.5 million people are in direct need of medical and humanitarian assistance. More than six million have been forced from their

homes and are now internally displaced due to shifting battle lines, armed groups and militia; and 4.3 million people are categorised as "hard to reach"—a humanitarian euphemism used when getting information from communities is limited, and as a result the likelihood of the population accessing sufficient protection, food, shelter, water or healthcare is extremely low.

The effects of war are not limited to frontlines or battle grounds. Indiscriminate bombings of civilians, hospitals and cities cause catastrophic blast injuries, permanent disability and deaths. War has insidiously crept into every consultation room, every hospital bed, health post and clinic in areas indirectly affected by the Syrian crisis over the last six years.

Médecins Sans Frontières (MSF) has tried to maintain operations throughout the country over the course of the conflict. Despite repeated requests for access to work in government-held areas, we have not been able to secure authorisation to do so. We can therefore only provide direct assistance and deploy teams in opposition-held territories and can mainly speak of what we see in those locations. These medical programmes are not classic by our definition. They have been forced to start and stop as the fighting draws near. They have been relocated after hospitals have been damaged by shells and mortar, or when the populations are forcibly displaced. These projects and hospitals operate all the time under impossible conditions with new staff, new systems, rapidly changing security management and dramatic variability of the availability of medicines and supplies as unpredictable border controls change from week to week. It is no easy feat to provide meaningful healthcare care in such an environment.

What we can describe from the numbers and experience generated from these programmes is indicative of a grave medical situation and looming public health crisis. At the most practical level, there are not

enough doctors, nurses or midwives in northern Syria. Most have fled, many have been killed and the future health workers have long since had their studies disrupted. There are not enough functioning health facilities at primary, secondary or tertiary level. There are also not enough medical supplies making their way across the international borders.

In regards to the population's health, we see gains in child health outcomes demonstrated in pre-war Syria slowly slipping away. Vaccination rates are at an all-time low, with MSF's survey of children in Northern Syria revealing only 17% had received their complete childhood immunisation schedule by the time they had reached the age of five. We know that Syrian children still do not receive the pneumococcal vaccine, which would considerably reduce to the incidence of paediatric pneumococcal pneumonia infections, a vital prevention strategy where antibiotics and access to clinics and hospital care in conflict settings is fraught. We have witnessed multiple and recurrent outbreaks of polio, measles and typhoid plaguing the children across the country causing severe illness and contributing to entirely preventable deaths. We have seen children born through the course of the conflict with congenital abnormalities or common paediatric problems who die or remain uncared for because the services and specialised care they need no longer exists or is inaccessible to them.

Women's access to functioning reproductive health care services is too low. It is so low hardly any women are attending routine antenatal care. Women in labour are forced to deliver at home as the birthing services no longer exist. There is evidence that those few functioning facilities that do offer emergency obstetric surgery have seen a significant surge in the number of women

electing to have unindicated caesarean sections, at great financial cost and unnecessary risk, rather than accept the risk of delivering at home. All around is evidence of worsening malnutrition among infants, as formula milk costs exceed what families can afford, and poor infant feeding practices due to lack of support and education programs.

The absence of health facilities means that those people living with chronic diseases such as diabetes, heart disease, renal disease, thalassemia, epilepsy and asthma report experiencing unabated symptoms. This group of patients' long-term disease progression, life expectancy and the later catastrophic burden on the future health system is yet to be seen.

There are many people suffering from the psychological effects of trauma, grief, loss, depression and anxiety, with very few places to get care. Many mothers tell us their children are angry or withdrawn, or have resumed bed wetting. Husbands and wives fight more than before. Hope is diminished, and people remain uncertain and fearful of the future.

For six years, the war has robbed the Syrian people of their right to health care. Poor politics and failed diplomacy have enabled the war to continue remorselessly and kept borders closed, taking away the rights of the Syrian people to flee the horrors and preventing medical humanitarian actors like MSF to access and support those most in need.

Médecins Sans Frontières doesn't have all the numbers. We just see those suffering and dying in front of our eyes. Many more individuals and families will continue to suffer unless this war stops. One more life is too many; collectively we need to do more to not only stop the war but to help those who are suffering.

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**Competing interests:**

Nil.

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# Patient response to use of tyrosine kinase inhibitors in lung cancer: a retrospective audit during funding changes

Anne Fraser

## ABSTRACT

**BACKGROUND:** The New Zealand Pharmaceutical Management Agency (PHARMAC) approved funding of erlotinib in October 2010 as second line therapy in all non-squamous non-small cell lung cancer after platinum-based chemotherapy with no requirement for epidermal growth factor (EGFR) mutation testing. Funding widened in August 2012 to include gefitinib as first line treatment for patients with a proven EGFR mutation. Then in January 2014, both tyrosine kinase inhibitors (TKIs) were approved for first line treatment, but only for disease with EGFR mutation.

**AIM:** To report the clinical experience with TKIs in a New Zealand tertiary referral centre over a period of funding change.

**METHOD:** Retrospective audit of all patients commenced on erlotinib from 1<sup>st</sup> October 2010 until 1<sup>st</sup> November 2011, and gefitinib from 1<sup>st</sup> August 2012 until 31<sup>st</sup> August 2013. Follow-up was two years for both groups.

**RESULTS:** Each group had 42 patients. Median Progression Free Survival was 76 days in the erlotinib group and 255 days in the gefitinib group. Twenty-eight percent of erlotinib patients had grade 3 adverse events with one treatment related death; fourteen percent of gefitinib patients had grade 3 adverse events. Dose reduction or treatment breaks were required in 12% in each group.

**CONCLUSION:** Response rate in these audits appear to reflect the change in funding criteria, with improved response rates likely to be associated with more targeted treatment.

Lung cancer is the leading cause of cancer-related death in New Zealand associated with an estimated 1,800 deaths per annum.<sup>1</sup> Systemic treatment with chemotherapy over the last 20 years has improved overall response rates, progression free survival and quality of life for patients in the advanced lung cancer setting.<sup>2-4</sup> The discovery of signalling pathway regulation for cell differentiation and proliferation has dramatically altered the treatment offered for advanced stage non-small cell lung cancer in the adenocarcinoma sub group. Identification of the epidermal growth factor receptor (EGFR) signalling pathway demonstrated that over-expression of EGFR influenced treatment outcomes in adenocarcinoma lung cancers.<sup>5</sup> The position of

the EGFR mutation on the exon of the DNA or RNA can also influence response to a tyrosine kinase inhibitor therapy (TKI). The rate of EGFR mutation is 20% internationally, whereas modelling suggested that the mutation rate might be as high as 40% in the New Zealand population.<sup>6</sup> Identifying this group of patients allows delivery of targeted treatment and improves outcomes.

Prior to the funding of a TKI in New Zealand, patients with advanced stage IV lung cancer received treatment with a regimen of a platinum-based doublet as per international guidelines, regardless of EGFR status.<sup>2</sup> Clinical trials demonstrated a clear benefit in both progression-free survival and overall survival for patients

with an EGFR mutation when treated with a TKI.<sup>7-10</sup> However, the New Zealand agency PHARMAC decided in 2010 that they would fund the TKI erlotinib following failure on a platinum doublet, regardless of EGFR mutation status. In 2012, PHARMAC undertook further review, including information and advice from the National Health Committee. The National Health Committee assesses the clinical safety and effectiveness of technology, such as gene mutation testing for predicting response to treatments. They recommended to PHARMAC that cytology labs carry out testing prior to use of a TKI in the non-squamous non-small cell lung cancer cohort to identify patients who were most likely to respond to the therapy in keeping with best international practice.<sup>5-10</sup> This recommendation resulted in the funding criteria shifting to include only those adenocarcinoma patients with a proven EGFR mutation in the first-line treatment setting.

The primary objective of this audit was to understand better the use of these novel agents in a New Zealand tertiary hospital over a period of funding change, and to assess length of progression free survival, overall survival, toxicities and response by exon mutation where known.

### Patients and methods

Two retrospective audits were completed. The first cohort consisted of all patients identified from hospital records that had commenced on erlotinib therapy following funding approval by PHARMAC in October 2010, until November 2011. This first cohort

contained patients with histologically or cytologically confirmed non-resectable, stage IV non-small cell lung cancer. All patients in this cohort had received at least one line of platinum-based chemotherapy, and had subsequent disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST) (Table 1).<sup>11</sup> There was no requirement for EGFR mutation testing, for this cohort. The first cohort received oral erlotinib 150mg daily until unacceptable toxicity, disease progression or death.

The second cohort consisted of all patients identified from hospital records that had commenced on gefitinib therapy from August 2012, when funding became available in the first line treatment setting, to August 2013. This second cohort contained only treatment naïve patients and those patients with a histologically or cytologically confirmed diagnosis of stage IV adenocarcinoma, who had then gone on to test positive for an EGFR mutation. At this time, exclusion of any patient with a histologically or cytologically confirmed diagnosis of squamous cell lung cancer from EGFR testing and subsequent targeted therapy treatment was routine. The second cohort received oral gefitinib 250mg daily until unacceptable toxicity, disease progression or death.

### Data collection and analysis

Demographic information collected over two years included age, gender, ethnicity, smoking status, exon mutation site where available, and performance status to quantify patient's general wellbeing using

**Table 1:** Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1.<sup>11</sup>

Response	Description
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

**Table 2:** European Cooperative Oncology Group Performance scoring tool.<sup>12\*</sup>

Grade	Definition
0	Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction)
1	Symptomatic but completely ambulatory (Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2	Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3	Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5	Death

\*Performance status is an attempt to quantify cancer patients' general well-being and activities of daily life. This measure is used to determine whether they can receive chemotherapy, whether dose adjustment is necessary and as a measure for the required intensity of palliative care.

the Eastern Cooperative Oncology Group (ECOG) assessment tool (Table 2).<sup>12</sup>

Non-demographic data fields collected included start and stop date of treatment, dose modifications and adverse events, as identified from the patient's clinical records and pharmaceutical history. In both audits, complete and partial responders were those patients identified by application for funding following restaging Computed Tomography (CT) reported by a radiologist, in keeping with PHARMAC guidelines.<sup>13</sup> Progression Free Survival was determined from the date of commencing the targeted therapy until the date of the documented progression on CT reporting. Patients received a restaging CT to assess for response within six weeks

of commencing their targeted therapy. This timing aligned with best practice from the literature, which indicates that assessment for response can be as early as one to two weeks of commencing a targeted therapy.<sup>14</sup> CT identified any response to the TKI, and the radiological report confirmed response, stable disease or progression. This report guided clinicians to continue or stop treatment. Clinicians assessed adverse events using the Common Terminology Criteria for Adverse Events Tool Version 4.3.<sup>15</sup> This assessment tool assists clinicians in grading side effects or adverse events associated with treatment (Table 3). Clinicians were then able to identify appropriate treatment courses, such as stopping therapy.

**Table 3:** Common Technology Criteria for Adverse Events Tool (version 4.3).<sup>14</sup>

Grade	Severity	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate	Minimal, local or non-invasive intervention indicated limiting age-appropriate instrumental ADL.*
Grade 3	Severe or medically significant but not immediately life-threatening	Hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL.**
Grade 4	Life-threatening consequences	Urgent intervention indicated.
Grade 5	Death related to adverse event	

Activities of Daily Living (ADL)\*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

\*\*Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

**Table 4:** Baseline characteristics of patients in cohort one (erlotinib n=42) and cohort two (gefitinib n=42).

		Erlotinib		Gefitinib	
		n	(%)	n	(%)
<b>Gender</b>	Male	20	(48)	22	(52)
	Female	22	(52)	20	(48)
<b>Age</b>	Median (IQR)	63 (56–78)		66 (61–78)	
<b>Ethnicity</b>	New Zealand European	21	(50)	18	(43)
	Māori	3	(7)	3	(7)
	Pacific Island	5	(12)	3	(7)
	Asian	9	(21)	11	(26)
	Other	4	(10)	7	(17)
<b>Smoking status</b>	Current	8	(18)	4	(9)
	Never	20	(48)	10	(24)
	Ex	12	(29)	8	(19)
	Not recorded	2	(5)	20	(48)
<b>ECOG scoring for performance status*</b>	0	0	(0)	6	(14)
	1	1	(2)	7	(17)
	2	2	(5)	3	(7)
	3	3	(7)	0	(0)
	4	1	(2)	2	(5)
	Not stated	35	(84)	24	(57)
<b>Histology</b>	Adenocarcinoma	38	(90)	42	(100)
	Squamous cell	4	(10)	0	(0)
<b>Previous lines of therapy</b>	None	0	(0)	42	(100)
	1	37	(88)	0	(0)
	2	3	(7)	0	(0)
	3	2	(5)	0	(0)

Survival data was analysed using Kaplan-Meier, with Minitab version 17 software. The measure of central tendency chosen for this analysis was the median, as the data was not symmetrically distributed. Inter-quartile range assessed spread.

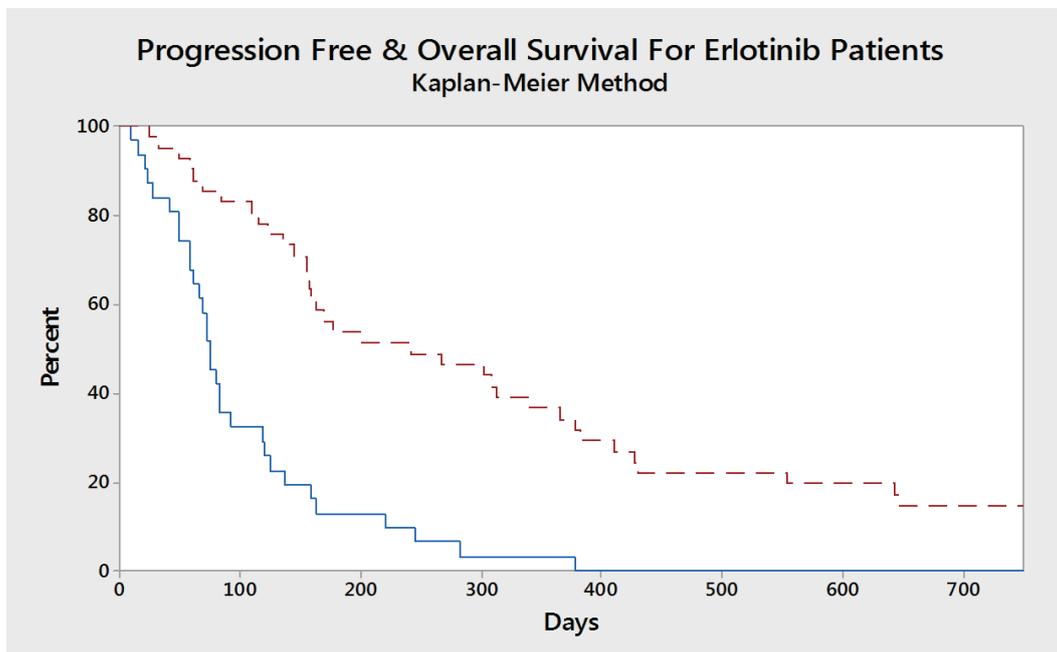
## Results

Forty-two patients in each audit met the inclusion criteria. The demographic data is summarised in Table 4.

There was equal distribution of male and female sex in both cohorts. Ethnicity was predominately New Zealand European, with the next biggest ethnic group identifying as

Asian. The median ages were similar. Documentation of smoking status in the erlotinib cohort was not present in all patients. Nine patients (21%) were smokers, 19 patients (45%) were never smokers and 12 patients (29%) were ex-smokers. Documentation of smoking status in the gefitinib cohort was not present in all patients. Four patients (9%) were smokers, 14 patients (33%) were never smokers and 7 patients (17%) were ex-smokers. The performance status scores of patients general wellbeing (ECOG score Table 3<sup>12</sup>) was not available for all patients in either cohort. In the erlotinib cohort, only one patient had an ECOG of zero. Two patients (5%) had an ECOG of two, and three

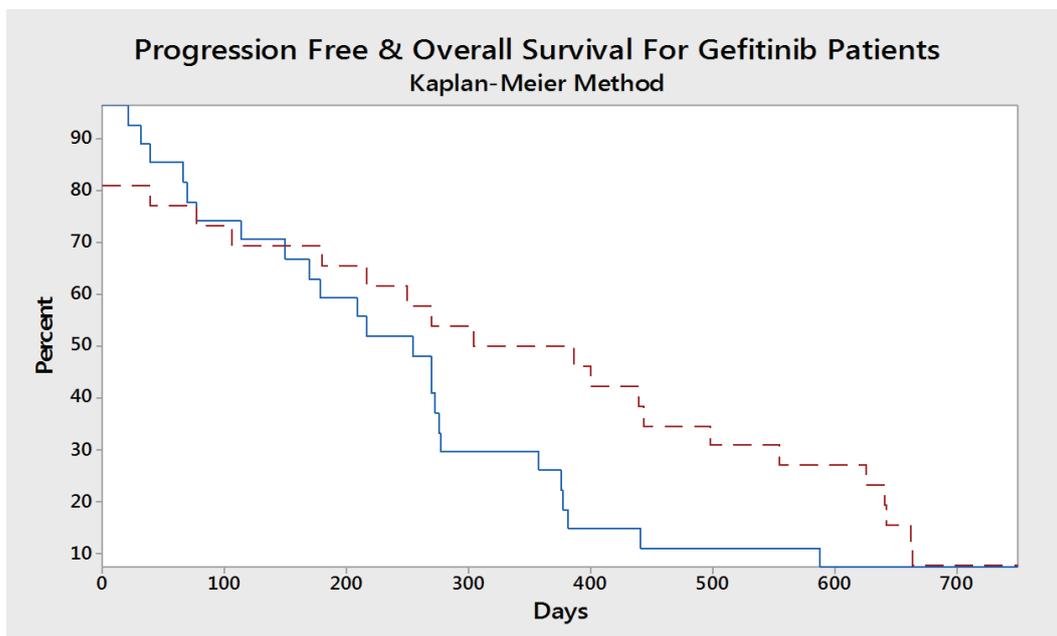
**Figure 1:** Progression-free survival (continuous line) and overall survival (broken line) (measured in days) for erlotinib patients. Censored at 730 days.



patients (7%) had an ECOG of three. In the gefitinib cohort, five patients (12%) had an ECOG of zero or one, three patients (7%) had an ECOG of three, and four patients (9%) had a reported ECOG of four. All 42 patients in the erlotinib cohort had received prior treatment, with 37 patients (88%) having received at least one prior line of therapy. All patients were treatment naive in the gefitinib cohort.

Median progression-free survival for the erlotinib group was 76 days, with an IQR of 125 days. The median overall survival for the erlotinib group was 242 days, with an IQR of 291 days (Figure 1). The median progression-free survival for the gefitinib group was 255 days with an IQR of 299 days. The median overall survival for the gefitinib group was 304 days, with an IQR of 549 days (Figure 2).

**Figure 2:** Progression-free survival (continuous line) and overall survival (broken line) (measured in days) for gefitinib patients. Censored at 730 days.



Response by exon mutation was available in 98% of cases in the gefitinib cohort, but none in the erlotinib cohort. Our results demonstrate patients with an exon 19 mutation had the longest progression-free survival at the nine month CT scan, with five patients (28%) still responding on CT. Patients with an exon 20 mutation had a poor response at the three-month CT scan, with only one patient demonstrating response. There were no responders in patients with mixed exon mutations at the three-month CT. Exon mutation was unknown in one patient.

Both cohorts expressed well-documented serious adverse events, including rash, diarrhoea, interstitial lung disease, deranged liver functions, fatigue and anorexia (Table 5). Fourteen (33%) of the erlotinib cohort required hospitalisation or a break from treatment to manage these events. Of the subgroup, 11 (80%) remained on a reduced dose and one (9%) required more than one break off treatment. Six (14%) of the total cohort stopped erlotinib due to toxicity.

Twelve (28%) of erlotinib patients had a grade three or four serious adverse event, including one treatment-related death. A summary of these events (Table 5) include diarrhoea, rash, nausea and deranged liver functions. Six (14%) of gefitinib patients had a grade three serious adverse event, including interstitial pneumonitis, acne form rash and raised liver function tests. Five (12%) of the cohort required hospitalisation or a break from treatment to manage these events. Of the subgroup, four (66%)

remained on a reduced dose. Of this total cohort, two patients (4.7%) stopped gefitinib treatment due to toxicity. A dose reduction or break was required in 12% of patients in each cohort.

## Discussion

These results are the first reported experience of TKI use in non-small cell lung cancer in New Zealand. Progression free and overall survival reflects the impact of the funding criteria, with initial funding not targeting those most likely to benefit. Funding then targeted patients with mutations who were more likely to respond to treatment, with improved survival rates reflected in the shift in funding criteria.

The first cohort in our study showed similar responses to congruent international studies using erlotinib. Median progression-free survival was 3.1 months in our cohort, while median overall survival was 5.7 months. A multicentre study of over 700 patients demonstrated a median 2.2-month progression-free survival and median 6.7-month overall survival in patients being treated with erlotinib.<sup>7</sup> Patients in this study had to have received at least one line of systemic therapy prior to recruitment and the EGFR status of patients was unknown at the time of recruitment. Another study that recruited over 6,500 patients found median progression-free survival and overall survival times were 3.3 months and 7.9 months respectively in the same cohort of patients.<sup>16</sup>

**Table 5:** Incidence rates of grade three+ adverse events by Common Terminology Criteria for Adverse Events.<sup>19</sup>

	Erlotinib n=42		Gefitinib n=42	
	n	(%)	n	(%)
Rash	8	(19)	8	(19)
Diarrhoea	6	(14)	2	(5)
Interstitial lung disease	0		1	(2)
Fatigue	1	(2)	2	(5)
Anorexia	0		1	(2)
Deranged liver functions	1	(2)	1	(2)
Dose reduction	5	(12)	5	(12)
Stopping treatment due to toxicity	6	(14)	2	(5)
Death	1	(2)	0	

The second cohort showed similar responses to congruent international trials. A multicentre phase three trial that recruited over 1,200 patients found a median progression-free survival of 5.7 months, with a median overall survival of 18.6 months in patients on gefitinib versus standard chemotherapy.<sup>17</sup> A smaller study of 230 patients with known EGFR status, randomly assigned to gefitinib or standard chemotherapy, reported a median progression-free survival of 10.8 months, with a median overall survival of 30.5 months in the gefitinib group.<sup>18</sup> Our progression-free survival results sit between these studies, with a median of 8.5 months. Our overall survival rate is low sitting at 10 months when compared to these international studies, though the demographic data is similar. Further lines of therapy available overseas may contribute to this. In both our cohorts, as with the international studies, identifying the time of actual progression was not possible, as assessments occurred at regulated times leading to an estimation of the event progression.

Knowledge of where the mutation sits enables clinicians to make choices on treatment options. Activating mutations for

EGFR present on the first four exons,<sup>18-21</sup> of the tyrosine kinase domain. Deletion mutations account for 44% of all EGFR mutations, and 41% are single point mutations. Within these four classes, 90% of mutations sit at the exon 19 or L858R sites.<sup>19-21</sup> Studies identify links between mutations harboured on the exon 20 insertion and insensitivity to targeted therapy, suggesting these patients may benefit from chemotherapy first line.<sup>19-21</sup> Our results reflect these findings that demonstrate the best responders are patients with an exon 19 or exon 21 mutation. The exon 19 patients had the best progression-free survival at the nine-month CT of 28%. Patients with a mixed point mutation or with an exon 20 mutation demonstrated insensitivity or resistance to TKI, with no responders in the mixed patient population and only one responder at the nine-month CT (14%) in the exon 20 mutation group.

Our results (Table 6) are comparable to the majority of international studies for incidence of adverse events,<sup>4,7,16,18,22</sup> with the exception of one larger international phase three trial that reported high numbers of diarrhoea, rash and anorexia in their gefitinib cohort.<sup>17</sup>

**Table 6:** Reported Serious Adverse Events by Common Terminology Criteria for Adverse Events.<sup>19</sup>

	Shephard (2005) <sup>7</sup> n=483 Erlotinib	Mok (2009) <sup>17</sup> n=607 Gefitinib	Maemondo (2010) <sup>18</sup> n=114 Gefitinib	Reck (2010) <sup>16</sup> n=6580 Erlotinib	Rosell (2012) <sup>4</sup> n=84 Erlotinib	Wu (2011) <sup>25</sup> n=110 Erlotinib	Gefitinib Cohort n=42	Erlotinib Cohort n=42
Rash	9%	66%	5.3%	<1%	13%	6.4%	19%	4.7%
Diarrhoea	6%	46.6%	0.9%	2%	5%	1.8%	4.7%	14%
Interstitial lung disease	<1%	2.6%	2.6%	<1%			2.3%	
Fatigue			2.6%		2%	0.9%	4.7%	2.3%
Anorexia	19%	22%	5.3%	<1%	6%		2.3%	
Deranged LFTs	9%		26.3%	<1%			2.3%	2.3%
Dose reduction	19%			17%			12%	12%
Stopping treatment due to toxicity	5%	GG		5%		19.1%	4.7%	14%
Death	0.2%	3.8%	0.8%	0.03%		2.7%		2.3%

Consideration of clinician experience with targeted therapies is important when looking at side effects between the two cohorts. In the first cohort of patients on erlotinib, clinicians were novices regarding the management of adverse events and more readily reported events when compared to the second cohort. However, overall reporting varied greatly between clinicians, and depended on the event. Documentation of grade one and two adverse events was poor in the clinical notes for both cohorts, as patients did not require a break from treatment, and therefore not reported in this study. Patient reporting was also variable, influenced by the education the patient had received prior to starting the erlotinib therapy. A good example of variable reporting and subsequent management was of acne form rash. There is evidence in the literature demonstrating a correlation between the severity of an acne form rash and positive treatment response.<sup>23</sup> Clinicians often relayed the correlation, influencing patient's beliefs on self-reporting of a rash. Patients stated that they were relieved to get a severe rash, and did not want to report this event believing the clinician would reduce the dose of the medication. Rash may also be related to toxicity and the poor excretion of the medication, and so education of patients is important. Patients were also less likely to report diarrhoea, describing embarrassment related to this side effect. Late reporting of diarrhoea resulted in hospitalisation, and in one case, perforation and death. Through treating the erlotinib cohort, clinicians were better prepared to manage the medications and the patients when the targeted therapy gained funding in the first line setting eighteen months later. Subsequently there was a reduction in adverse events reported, reduced hospital admissions and reduced number of patients needing to discontinue medication in the gefitinib group.

A major limitation of this audit is the difference in treatment criteria between the two cohorts and its influence on response. Pre-treatment with chemotherapy in the first cohort may have caused injury to the kidneys, liver and bone marrow, affecting the metabolism and excretion of other medications and affecting toxicity. Patients were treatment naïve in the second cohort

and therefore more likely to tolerate the TKI. The results reflect this heterogeneity, and should not be considered causative, but rather demonstrate the likely influence of targeting treatment. However, at the first review point (within three months of commencing therapy) the erlotinib group did demonstrate a response rate of 48%. Such a response suggests that patients who have been pre-treated may still benefit from a second line, targeted therapy and that a wider range of patients, including EGFR wild-type patients, may benefit from a targeted therapy. New Zealand's current funding model does not include either of these patient groups.

A further limitation of these audits was the criteria used to define response. Progression-free survival was determined from the date of commencing the targeted therapy until the date of the documented progression utilising PHARMAC criteria and CT reporting rather than the use of RECIST (Table 1).<sup>11</sup> In usual practice, clinicians would utilise RECIST response criteria to assess for disease progression on radiology.<sup>11</sup> This was not the requirement for renewal of PHARMAC funding; the pseudo-criteria became the impression documented on the CT report. Radiology reports might demonstrate progression, but once submitted to the RECIST calculator, they did not meet the criteria outlined in 4.3 of the guidelines to confirm progression. Such patients should be eligible to continue funded targeted therapy, though had to discontinue TKI in our setting in keeping with the PHARMAC criteria.

Finally, the results of these audits provide lessons for the role of future molecular testing. Positive impacts on clinical outcomes occur when testing for mutations happens as part of routine practice, demonstrated above. Extending the idea of testing to gain the best clinical outcomes for patients is an important consideration for funders and providers, with new generations of targeted therapies and immunotherapies becoming available. A current example is the presence of T790M expression for patients who have developed a resistance to their tyrosine kinase inhibitor, with early clinical trials indicating a better response to some immunotherapies in patients with this T790M mutation.<sup>24</sup>

## Conclusion

Progression free and overall survival in both cohorts reflects the impact of the funding criteria. Initially funding targeted treatment failure following first line chemotherapy. Once funding was introduced targeting patients with EGFR mutations, who were more likely to respond to treatment, progression free and overall survival

improved in line with international trials. Reports of serious adverse events in our two cohorts reflect those outcomes reported in larger international studies. Gathering further information around patients' comorbidities and the affect these may have on toxicities, compliance and outcomes will help to define further the patient experience to targeted therapies.

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### Competing interests:

Nil.

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# Missing data on body mass index in a breast cancer register: how is it associated with patient characteristics and clinical outcomes?

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## ABSTRACT

**AIM:** To assess the completeness of data on body mass index (BMI) in a regional breast cancer register, and its association with patient characteristics and clinical outcomes.

**METHODS:** This analysis used the data from the Waikato Breast Cancer Register and involved all women who were diagnosed with primary breast cancer in the Waikato District Health Board Region between January 2000 and June 2014. Patients with recorded BMI were compared with those with missing data in terms of demographics, disease factors and treatment factors. Cox regression modelling was performed, and hazards of specific outcomes associated with missing data on BMI were assessed.

**RESULTS:** Of the 3,536 patients included in this analysis, 27.4% had missing data on BMI. Missing data was more frequent in older patients, rural dwellers, patients with comorbidities, screen detected patients, patients with early stage or low grade cancer and hormone receptor positive patients, but was minimal in patients who received chemotherapy. Patients with missing data were less likely to experience loco-regional recurrence (although not significant), metastasis and breast cancer specific mortality, but more likely to experience death from other causes even after demographic, disease and treatment factors were adjusted.

**CONCLUSIONS:** Height or weight or both were not recorded for more than one quarter of the patients. Missing data was differential by specific patient characteristics and clinical outcomes.

Breast cancer is the most common cancer in New Zealand women, accounting for almost 30% of all new cancer cases and 14% of all cancer deaths in 2012, with a higher rate observed in Māori, Pacific women and those living in deprived area.<sup>1,2</sup> New Zealand has poorer survival from breast cancer compared to some other developed nations,<sup>3</sup> including its neighbour Australia.<sup>4,5</sup>

The outcomes of breast cancer can be influenced by a range of factors, including demographic, biological and treatment factors. One important factor is obesity, assessed by body mass index (BMI, weight/height<sup>2</sup>). A meta-analysis of 82 studies reported an increased risk of total mortality with a hazard ratio of 1.41 (95% CI: 1.29-1.53) for women with a BMI over 30 compared to those with normal weight (BMI 18.5-25.1).<sup>6</sup> While a few studies have shown

no effect, most studies show worse outcomes in patients with higher BMI, including metastatic disease and first recurrences.

In New Zealand, three in ten adults are obese, and the rate is significantly higher in Māori, Pacific women and those living in deprived areas.<sup>7</sup> Yet the ability of researchers to explore the contribution of BMI to breast cancer outcomes is limited, as the national and regional cancer registries do not routinely collect information on patient height and weight, although some regional registries have started collecting the data recently. An exception is the Waikato Breast Cancer Register, which captures newly diagnosed breast cancer cases in the Waikato District Health Board Region, and has recorded patient height and weight at the time of diagnosis since 1991.

This paper assessed the completeness of data on patient height, weight and BMI in the Waikato Breast Cancer Register and its association with specific patient characteristics and clinical outcomes.

## Methods

### Data sources

This analysis used the data from the Waikato Breast Cancer Register and involved all women who were diagnosed with primary breast cancer in the Waikato District Health Board Region between January 2000 and June 2014. Compared with the national data sources, the register contains more comprehensive and accurate information on many factors,<sup>8,9</sup> and records patient demographics such as age, ethnicity and health domicile code, height, weight, year of cancer diagnosis, mode of presentation (screen or symptomatic), tumour characteristics such as stage at diagnosis, grade, histological type and hormone receptor status, treatments undertaken such as surgery, radiotherapy, chemotherapy, hormonal therapy and biological treatment and health care facility where primary treatment was undertaken. Information on patient height and weight was obtained from the medical oncology new patient clinical letter or the surgical admission form or both, which record measured weight. If such information was not available, the patient history form was used, which records measured or self-completed (with help from a nurse) height and weight. The health domicile codes represent patients' usual residential address, and were categorised as urban (main urban, satellite urban and rural with high urban influence) and rural areas (others) based on Statistics New Zealand's Urban/Rural Profile.<sup>10</sup> To assess the degree of neighbourhood deprivation, the domicile codes were also mapped on to the 2006 New Zealand Deprivation Index (NZDep),<sup>11</sup> with decile ten the most deprived and decile one the least. Each woman was followed prospectively through public and private clinic follow-ups, and outcomes such as loco-regional recurrence, metastasis and death were recorded.

The data were linked to the National Minimum Dataset (NMDS) to obtain information on comorbidities. The NMDS

contains information about all day patients and inpatients discharged from all public hospitals and over 90% of private hospitals in New Zealand.<sup>12</sup> Comorbidity was measured using a C3 index score, which is a cancer-specific index of comorbidity based on the presence of 42 chronic conditions recorded in the NMDS for a period of five years prior to the diagnosis of cancer.<sup>13</sup> Each condition was weighed to its impact on one-year non-cancer mortality in a cancer cohort, and the weights were then summed to get a final comorbidity score.

This analysis was undertaken as part of a wider project aiming to improve outcomes for women with breast cancer in New Zealand. Ethical approval for the project was obtained from the New Zealand Northern 'A' Ethics Committee (Ref. No. 12/NTA/42).

### Analyses

All analyses were performed using SAS (release 9.4, SAS Institute Inc., Cary, North Carolina). Missing values except for BMI were computed using multiple imputation with ten complete datasets created by the Markov chain Monte Carlo method,<sup>14</sup> incorporating all baseline characteristics and outcomes. Baseline data were presented as percentages, and compared between patients with recorded height, weight and BMI and those with missing data by using a  $\chi^2$  test.

Cumulative incidences for specific outcomes (loco-regional recurrence, metastasis, breast cancer-specific mortality, death from other causes and overall mortality) in the presence of competing risks were computed. For loco-regional recurrence and metastasis, death from any cause as the first event was considered as a competing risk. For breast cancer-specific mortality, death from other causes as the first event was considered as a competing risk. For death from other causes, breast cancer-specific death as the first event was considered as a competing risk. Cox proportional hazards regression modelling was then performed and hazards of the specified outcomes associated with missing data on BMI were assessed. Hazard ratios (HRs) were adjusted for all baseline characteristics except HER-2 status (as about one-third of the records had missing values).

## Results

There were 3,536 patients who were diagnosed with primary breast cancer between January 2000 and June 2014. Height was not recorded on 25.4% of patients and weight not recorded on 16.2% so that BMI was unavailable for 27.4% (Table 1). There were significant differences in baseline characteristics of patients with recorded vs. unrecorded height, weight and BMI. Generally, missing data was more frequent in patients who were older and of European

ethnicity, resided in semi-urban or rural areas and had a higher comorbidity index. Missing data was also more common in screen-detected patients, patients with early stage (0 and 1) or low-grade cancer and hormone receptor-positive patients. BMI information was available on almost all patients who had adjuvant chemotherapy but was missing on about 40% of other patients. The amount of missing data has declined over time but was still 17.1% in the most recent period, 2012–14.

**Table 1:** Baseline characteristics of patients by missing height, weight and BMI.

Characteristics	Total	Height			Weight			BMI		
		Missing	%	p-value	Missing	%	p-value	Missing	%	p-value
<b>Total</b>	3,536	897	25.4		573	16.2		968	27.4	
<b>Age</b>										
<40	179	15	8.4	<0.0001	4	2.2	<0.0001	15	8.4	<0.0001
40–59	1,642	322	19.6		226	13.8		355	21.6	
60–79	1,367	385	28.2		242	17.7		416	30.4	
80+	348	175	50.3		101	29.0		182	52.3	
<b>Menopausal status</b>										
Pre-menopause	915	122	13.3	<0.0001	84	9.2	<0.0001	139	15.2	<0.0001
Peri-menopause	139	23	16.5		14	10.1		25	18.0	
Post-menopause	2,461	743	30.2		470	19.1		795	32.3	
<i>Missing/unknown</i>	21	9	42.9		5	23.8		9	42.9	
<b>Ethnicity</b>										
European	2,845	770	27.1	0.0001	503	17.7	<0.0001	832	29.2	<0.0001
Māori	534	98	18.4		56	10.5		106	19.9	
Pacific	60	13	21.7		4	6.7		13	21.7	
Asian	90	15	16.7		9	10.0		16	17.8	
Others	7	1	14.3		1	14.3		1	14.3	
<b>NZDep 2006</b>										
1–2	362	77	21.3	0.1	56	15.5	0.98	85	23.5	0.3
3–4	420	102	24.3		65	15.5		113	26.9	
5–6	781	199	25.5		131	16.8		214	27.4	
7–8	1,063	298	28.0		177	16.7		310	29.2	
9–10	878	212	24.1		139	15.8		234	26.7	
<i>Missing/unknown</i>	32	9	28.1		5	15.6		12	37.5	

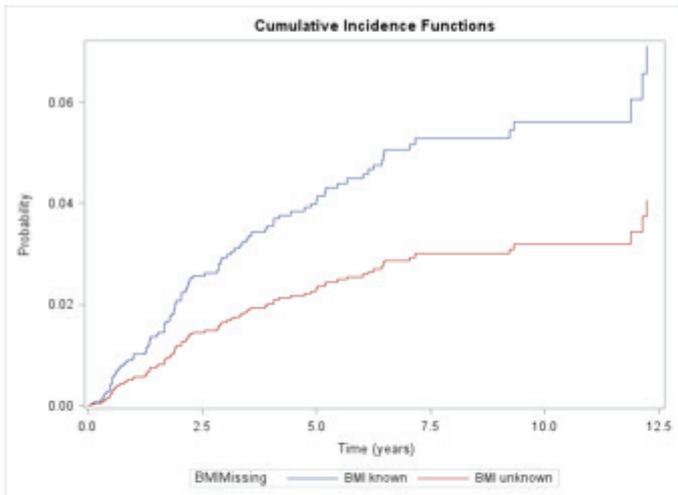
**Table 1:** Baseline characteristics of patients by missing height, weight and BMI (Continued).

<b>Area of residence</b>										
Urban	1,939	438	22.6	<0.0001	286	14.7	0.03	474	24.4	<0.0001
Semi-urban or rural	1,469	415	28.3		265	18.0		447	30.4	
<i>Missing/unknown</i>	128	44	34.4		22	17.2		47	36.7	
<b>C3 index score</b>										
0	2,737	611	22.3	<0.0001	421	15.4	0.04	669	24.4	<0.0001
1	311	99	31.8		56	18.0		105	33.8	
2	195	60	30.8		33	16.9		64	32.8	
3+	293	127	43.3		63	21.5		130	44.4	
<b>Screen-detected</b>										
Yes	1,441	408	28.3	0.0008	266	18.5	0.003	446	31.0	<0.0001
No	2,095	489	23.3		307	14.7		522	24.9	
<b>Stage at diagnosis</b>										
0	466	182	39.1	<0.0001	116	24.9	<0.0001	194	41.6	<0.0001
I	1,181	402	34.0		263	22.3		435	36.8	
II	1,240	223	18.0		131	10.6		241	19.4	
III	466	48	10.3		31	6.7		52	11.2	
IV	178	37	20.8		27	15.2		41	23.0	
<i>Missing/unknown</i>	5	5	100.0		5	100.0		5	100.0	
<b>Grade</b>										
I	736	253	34.4	<0.0001	174	23.6	<0.0001	278	37.8	<0.0001
II	1,682	387	23.0		237	14.1		423	25.1	
III	808	135	16.7		72	8.9		141	17.5	
<i>Missing/unknown</i>	310	122	39.4		90	29.0		126	40.6	
<b>Histology</b>										
Ductal	2,443	543	22.2	<0.0001	344	14.1	<0.0001	585	23.9	<0.0001
Lobular	336	66	19.6		47	14.0		83	24.7	
Other	750	100	13.3		175	23.3		293	39.1	
<i>Missing/unknown</i>	7	6	85.7		7	100.0		7	100.0	
<b>ER/PR</b>										
ER+/PR+	2,088	540	25.9	<0.0001	366	17.5	<0.0001	594	28.4	<0.0001
ER+/PR-	667	154	23.1		87	13.0		161	24.1	
ER-/PR+	34	5	14.7		3	8.8		6	17.6	
ER-/PR-	512	90	17.6		40	7.8		94	18.4	
<i>Missing/unknown</i>	235	108	46.0		77	32.8		113	48.1	

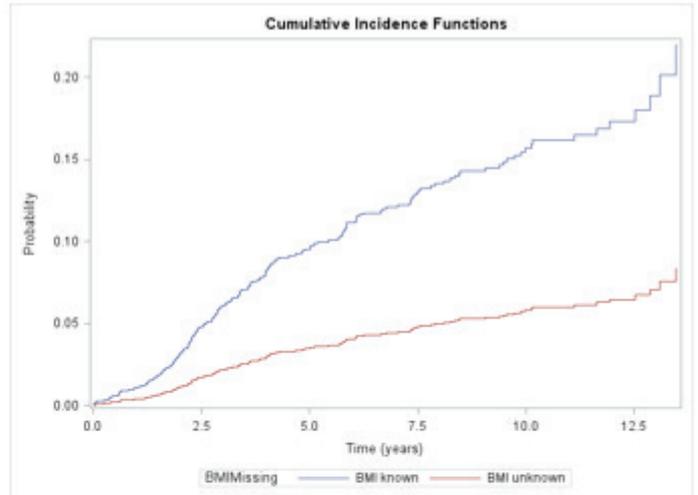
**Table 1:** Baseline characteristics of patients by missing height, weight and BMI (Continued).

<b>HER-2</b>										
Positive	475	55	11.6	<0.0001	24	5.1	<0.0001	57	12.0	<0.0001
Equivocal	178	71	39.9		41	23.0		76	42.7	
Negative	1,869	372	19.9		250	13.4		417	22.3	
<i>Missing/unknown</i>	1,014	399	39.3		258	25.4		418	41.2	
<b>Loco-regional treatment</b>										
Breast conserving surgery with radiotherapy	1,615	423	26.2	<0.0001	293	18.1	<0.0001	460	28.5	<0.0001
Breast conserving surgery without radiotherapy	395	131	33.2		79	20.0		139	35.2	
Mastectomy with radiotherapy	523	31	5.9		14	2.7		37	7.1	
Mastectomy without radiotherapy	718	200	27.9		100	13.9		213	29.7	
No primary surgery	285	112	39.3		87	30.5		119	41.8	
<b>Adjuvant treatment</b>										
Chemotherapy alone	345	6	1.7	<0.0001	2	0.6	<0.0001	6	1.7	<0.0001
Hormonal/biological therapy alone	1,500	520	34.7		330	22.0		563	37.5	
Chemotherapy and hormonal/biological therapy	727	11	1.5		4	0.6		12	1.7	
None	964	360	37.3		237	24.6		387	40.1	
<b>Facility where primary treatment was undertaken</b>										
Private	992	243	24.5	0.5	203	20.5	<0.0001	263	26.5	0.5
Public	2,544	654	25.7		370	14.5		705	27.7	
<b>Diagnostic year</b>										
2000–2002	579	195	33.7	<0.0001	110	19.0	<0.0001	197	34.0	<0.0001
2003–2005	719	324	45.1		181	25.2		328	45.6	
2006–2008	765	154	20.1		116	15.2		178	23.3	
2009–2011	754	116	15.4		89	11.8		142	18.8	
2012–2014	719	108	15.0		77	10.7		123	17.1	

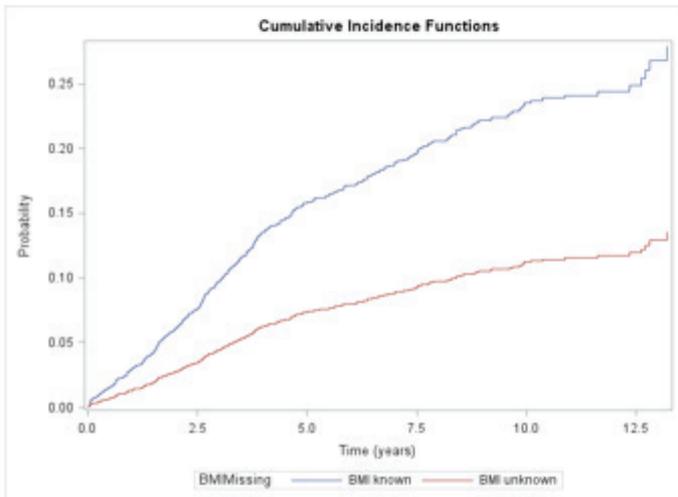
Figure 1: Cumulative incidence of specific outcomes in patients with known BMI vs. unknown BMI.



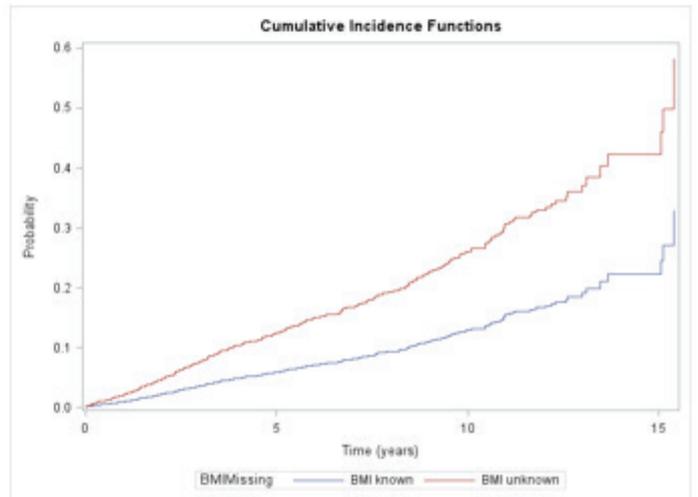
(a) Loco-regional recurrence



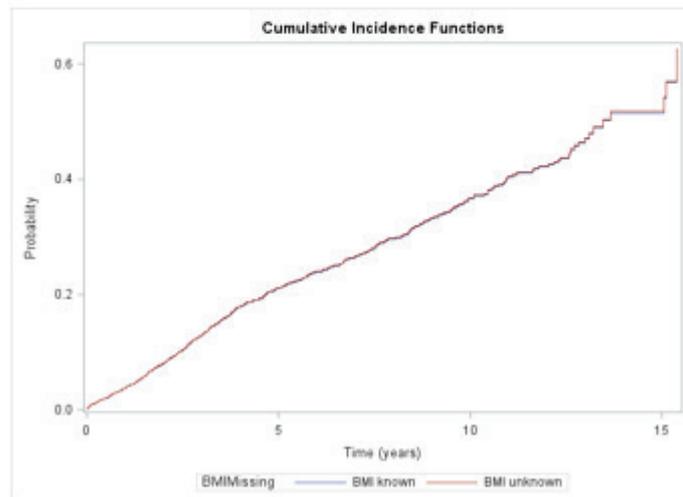
(b) Metastasis



(c) Breast cancer specific death



(d) Death from other causes



(e) Overall mortality\*

\* Figure 1 (e) has two lines which are overlapping.

Patients with missing data on BMI were less likely to experience loco-regional recurrence (crude HR: 0.56; 95% CI: 0.35, 0.90; adjusted HR: 0.61; 95% CI: 0.37, 1.02), metastasis (crude HR: 0.35; 95% CI: 0.24, 0.50; adjusted HR: 0.38; 95% CI: 0.25, 0.58) and breast cancer-specific mortality (crude HR: 0.44; 95% CI: 0.34, 0.57; adjusted HR: 0.64; 95% CI: 0.46, 0.88), but were more likely to experience death from other causes (crude HR: 2.19; 95% CI: 1.78, 2.70; adjusted HR: 1.28; 95% CI: 1.00, 1.63) (Figure 1 and Table 2). The HRs were adjusted for all baseline characteristics mentioned in Table 1, except HER2-status.

## Discussion

In the Waikato Breast Cancer Register, height was not recorded on one in four patients and weight not recorded on one in six patients. Missing data was differential by several demographic, disease and treatment factors as well as specific outcomes.

In general, patients with missing data were older, had early-stage cancer, did not receive chemotherapy and had better cancer-specific outcomes. It is possible that older patients were less likely to have their BMI measured or to complete height and weight fields in the patient history form, and hence had more missing data. It is not surprising that BMI data is almost complete for patients who received chemotherapy,

as BMI is important in the prescribing of chemotherapy. These patients also tend to have more aggressive cancer and hence have poorer outcomes. Importantly, our findings indicate that analyses restricted to patients with recorded BMI could be biased, possibly away from the null.

The amount of missing data in the register has been declining over time, reflecting efforts made by the registry staff to ensure that BMI data is collected. However, there is room for improvement as BMI was not available for about 17% of patients who were diagnosed between 2012 and 2014. Patient height and weight should be recorded in all population-based cancer registries for several reasons. First, obesity rates in New Zealand are among the highest in the OECD countries.<sup>15</sup> In particular, two in three Pacific women and one in two Māori women are obese.<sup>7</sup> Second, there is increasing evidence linking obesity to development and prognosis of breast cancer<sup>6,16</sup> and also several other cancers.<sup>17</sup> Possible mechanisms include hormonal imbalance, suboptimal treatment and related comorbidities,<sup>6,18,19</sup> and may be different across population subgroups (eg, across racial/ethnic groups<sup>16</sup>). Yet the impact of obesity on breast cancer has rarely been evaluated in New Zealand. Such evaluation would benefit Māori and Pacific women most, as they bear a disproportionate burden of obesity and related diseases including cancer.

**Table 2:** Clinical outcomes in patients with recorded vs. unrecorded BMI.

Outcome	BMI	Crude HR (95% CI)	Adjusted HR* (95% CI)
Loco-regional recurrence	BMI recorded	1.00	1.00
	BMI unrecorded	0.56 (0.35, 0.90)	0.61 (0.37, 1.02)
Distant metastasis	BMI recorded	1.00	1.00
	BMI unrecorded	0.35 (0.24, 0.50)	0.38 (0.25, 0.58)
Breast cancer specific death	BMI recorded	1.00	1.00
	BMI unrecorded	0.44 (0.34, 0.57)	0.64 (0.46, 0.88)
Death from other/unknown causes	BMI recorded	1.00	1.00
	BMI unrecorded	2.19 (1.78, 2.70)	1.28 (1.00, 1.63)
Overall mortality	BMI recorded	1.00	1.00
	BMI unrecorded	0.99 (0.87, 1.20)	1.03 (0.85, 1.25)

\* Adjusted for all baseline characteristics mentioned in Table 1 except HER2-status.

An initial step in New Zealand would be to routinely record height and weight in the NMDS, as hospital records are the primary source of information for cancer registries and contain data on objectively measured height and weight. An earlier US study found height and weight to be available in the hospital record of most cancer patients (more than 80%) at the time of diagnosis, but acknowledged that manually abstracting height and weight for each patient was resource-intensive.<sup>20</sup> However, the data collection process should be simpler, quicker and cheaper with the growing movement toward electronic health records, advances in data linkage and availability of digital medical scales, which can be connected to a PC or smartphone.

Potential limitations of this analysis should be noted. Misclassification of the cause of death may occur, but such errors are likely to be similar in the two groups being compared, and will only act to reduce observed differences to a small extent.

NZDep2006 used in this analysis measures area-level deprivation and may not reflect an individual's actual socioeconomic status, although it has been validated previously.<sup>21</sup> Tumour grade and ER/PR status were missing for some patients (9% and 7% respectively) as patients with stage 0 or in-situ cancer were included in this analysis. HER-2 status was missing for 29% of the patients and was excluded from this analysis, as most patients with missing HER-2 were diagnosed prior to 2006 when HER-2 testing was not routine in New Zealand.

To conclude, height or weight or both were not recorded for more than one quarter of the patients in the Waikato Breast Cancer Register. Importantly, missing data was differential by specific patient characteristics and clinical outcomes. To be able to evaluate the associations between BMI and breast cancer outcomes in New Zealand, patient height and weight should be recorded in hospital and computerised data systems.

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# Oral cancer risk factors in New Zealand

Muhammed Yakin, Ratu Osea Gavid, Brian Cox, Alison Rich

## ABSTRACT

Oral cancer constitutes the majority of head and neck cancers, which are the fifth most common malignancy worldwide, accounting for an estimated 984,430 cases in 2012. Between 2000 and 2010, there were 1,916 cases of OSCC in New Zealand with a male to female ratio of 1.85:1, and an age-standardised incidence rate of 42 persons per 1,000,000 population.

This article presents an overview of the main risk factors for oral and oropharyngeal cancers and their prevalence in New Zealand. Alcohol consumption is the most prevalent risk factor in New Zealand, followed by tobacco. Given the high prevalence of these two risk factors and their synergistic effect, it is important for doctors and dentists to encourage smoking cessation in smokers and to recommend judicious alcohol intake. Research is needed to determine the prevalence of use of oral preparations of tobacco and water-pipe smoking in New Zealand, especially due to changing demography and increases in migrant populations. UV radiation is also an important risk factor. Further investigations are also needed to determine the prevalence of oral and oropharyngeal cancers attributable to oncogenic HPV infection.

**H**ead and neck cancers are the fifth most common malignancy worldwide, accounting for an estimated 984,430 cases in 2012.<sup>1</sup> Head and neck cancers are cancers arising in the lips, oral cavity, nasal cavity, paranasal sinuses, pharynx, salivary glands and thyroid glands. Approximately half of the head and neck cancers occur in the oral and oropharyngeal regions.<sup>1</sup> There is confusion as to what lesions are classified as 'oral cancer', which poses difficulties when comparing different studies.<sup>2</sup> The term oral cancer generally refers to the malignancies of the oral cavity and lip vermilion,<sup>3-5</sup> 90% of which are oral squamous cell carcinomas (OSCC). In this paper oral cancer will refer to OSCC unless otherwise specified, and thus exclude cancers of the skin of the lips, the oropharynx, all salivary gland and connective tissue neoplasms as well as intra-osseous squamous cell carcinomas.

Between 2000 and 2010, there were 1,916 cases of OSCC in New Zealand, with a male to female ratio of 1.85:1 and an age-standardised incidence rate of 42 persons per 1,000,000 population from 2000 to 2010.<sup>6</sup> The age-specific incidence rates of OSCC steadily increased with age, whereas incidence was highest in the 6<sup>th</sup> decade of life (Figure 1). The most common site for OSCC was the

tongue, which accounted for over 40% of OSCCs, followed by the lip vermilion, which accounted for more than 20% of all OSCCs (Figure 2).

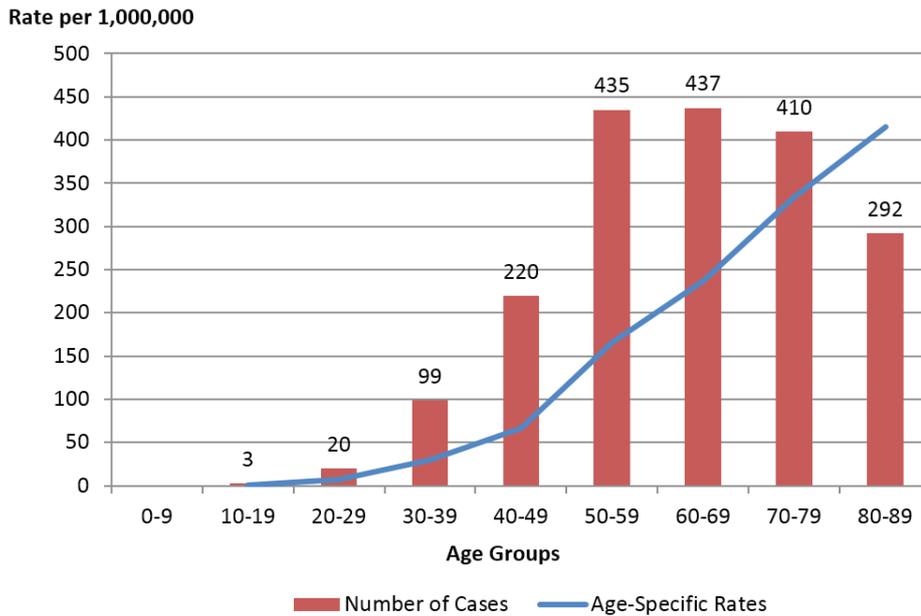
Oral carcinogenesis is a multi-step process that involves progressive genetic mutations affecting tumour suppressor genes and proto-oncogenes, resulting in uncontrolled cell proliferation. Modifiable lifestyle factors such as tobacco and alcohol consumption are considered to contribute in up to 75% of cases of OSCC.<sup>3,7</sup> In addition, a very small percentage of people have inherent genetic defects that make them prone to oral cancer.<sup>3,8,9</sup>

## Risk factors in New Zealand

Oral cancer risk factors are grouped according to decreasing levels of evidence supporting their carcinogenicity from established, strongly suggestive, possible and proposed (Table 1).<sup>3</sup> The traditional risk factors for oral cancer include tobacco, alcohol and betel quid use, whereas solar ultraviolet (UV) radiation is the main risk factor for cancer of the skin and vermilion of the lip.<sup>10-13</sup> Genetic damage from these risk factors tends to accumulate over many years, and hence OSCCs are more common

**Figure 1:** Average annual age-specific rates and total number of cases of OSCC in New Zealand between 2000 and 2010.

### OSCC in New Zealand, 2000-2010



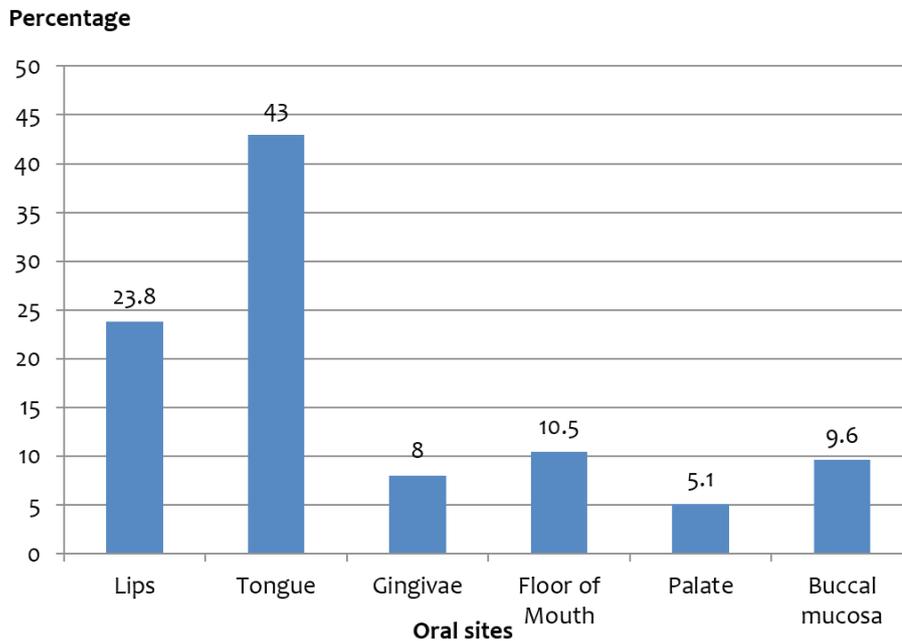
in people in their fifth to seventh decades of life than at younger ages.

For intra-oral cancer, the established group of risk factors includes tobacco, alcohol and betel quid chewing, whereas a very small subset are attributable to human papilloma virus (HPV) type 16.<sup>8,10,14,15</sup>

#### Tobacco

Tobacco use is a key risk factor for the development of oral cancer. Current smokers are at a four-fold increased risk of developing oral cancer compared with non-smokers, and heavy smokers are twenty times more likely to develop oral

**Figure 2:** The site distribution of OSCC in New Zealand.



**Table 1:** Risk factors for oral cancer grouped according to the level of evidence supporting their carcinogenicity (modified from Warnakulasuriya, 2009<sup>3</sup> and the IARC<sup>13</sup>).

Established	Strongly suggestive	Possible	Proposed
Smoking Chewing tobacco Alcohol consumption Betel quid chewing Human papilloma virus type 16	Sunlight (lip) Radiation	Human papilloma virus type 18 Immune deficiency	Mouthwashes Mate drinking Familial

cancers than non-smokers.<sup>10</sup> After five years of quitting tobacco smoking, the risk of developing oral and pharyngeal cancers appears to drop substantially.<sup>10</sup> Tobacco products fall into three main types: rolls, oral preparations and pipes. Rolls include cigarettes, cigars and hand-rolled tobacco products, and are the most common type of tobacco product in New Zealand. The prevalence of the use of pipes and oral preparations in New Zealand is unknown. Most of the available data regarding tobacco smoking in New Zealand refers to the use of cigarettes. There are approximately 4,000 chemicals in cigarettes, many of which are known carcinogens.<sup>16</sup>

According to the 2015 New Zealand Health Survey, the prevalence of smoking among New Zealand adults decreased from 18% in 2011–2012 to 17% in 2014–2015. In 2014–2015 the percentage of New Zealand adults who smoked daily was 15%. This percentage was highest in adults aged 18–34 years, where approximately one in four adults was a current smoker, whereas only 6% of those younger than 18 years were smokers. Generally, men (18%) were more likely to smoke tobacco than women (15%), but in the Māori population more women (42%) smoked tobacco than men (34%). Smoking rates were higher in more socio-economically disadvantaged areas. The latest data showed that 6% of Asian, 38% of Māori and 25% of Pacific adults were current smokers.<sup>17</sup>

The New Zealand Ministry of Health provides smoking cessation advice training to all healthcare professionals to support and encourage smokers to quit. A number of nicotine-replacement therapy products are subsidised for this purpose.<sup>18</sup> It is of utmost importance that doctors and dentists

are aware of the prevalence of tobacco smoking among different age groups in their clinic population in order to better provide patients with appropriate smoking cessation advice.

Electronic, or e-cigarettes, are used in some countries to help smokers quit. However, their safety is still a matter for debate. Research has shown that their use, regardless of nicotine content, induces apoptosis and necrosis in epithelial cells. The ability of e-cigarette smoke to induce double-strand DNA breaks and clonal proliferation in oral epithelial cells is also of concern.<sup>19,20</sup> E-cigarette use among New Zealand youths has tripled since 2012. In 2014, 20% of young people reported having ever used e-cigarettes.<sup>21</sup> Most adults reported they used e-cigarettes to help them quit, whereas most youths used e-cigarettes because they were curious. There is need for health education regarding the potential risks of e-cigarette use in New Zealand, especially among the young.

Some oral preparations also enhance contact of carcinogens with the oral mucosa. The most common example is betel quid, to which tobacco may also be added. The main ingredient of a betel quid is areca nut wrapped in a betel leaf, usually with slaked lime, with or without the addition of tobacco (Figure 3). The quid is placed in the mandibular buccal sulcus and chewed, producing a mild euphoric effect. Tobacco is an ingredient of the betel quid in some cultures, particularly in India and South East Asia and migrant populations from these regions. The regular use of betel quid, with or without tobacco may lead to the development of sub-mucous fibrosis, a potentially malignant oral disorder.<sup>9</sup> The use of betel quid without tobacco causes

**Figure 3:** Slaked lime, tobacco and areca nut on a betel leaf as a wrap. (Image credit: Mr Shremal Patel).



a three-fold increase in oral cancer risk in non-smokers and non-drinkers.<sup>12</sup> When used with tobacco, the risk rises to seven-fold in non-smokers and non-drinkers and to 12- to 22-fold in smokers and drinkers.<sup>12,22</sup> Very little data is available on the prevalence of use of these oral preparations in people of South East Asian origin now resident in New Zealand.<sup>23,24</sup> The Oral Pathology Diagnostic Service at the University of Otago has reported eight cases of oral submucous fibrosis from January 2005 to June 2016 from over 23,000 specimen accessions during that period, and all patients were of South-East Asian origin.

Another way to use tobacco products is pipe smoking. This includes direct pipe smoking through a wooden pipe, previously common in Western societies, but now uncommon. This category also includes water-pipe tobacco smoking, also known as shisha, nargileh and hookah. These are particularly popular social outdoor smoking activities in cafes and homes among Middle-Easterners. Water-pipe smoking consists of coals as a heat source often with flavoured tobacco that is smoked through water using pipes (Figure 4). The prevalence of water-pipe smoking in New Zealand is unknown. However, a study carried out in the Arabic-speaking population in south-west Sydney showed that one in four of over 700 participants reported that they smoked water-pipes.<sup>25</sup> It should be noted that the rate reported in the

Sydney study was much higher than that estimated worldwide among Arab youth in the Global Youth Tobacco Survey, where an average of 10.6% of Arab youth reported they were water-pipe smokers.<sup>26</sup> What is more concerning is the popular belief that water-pipe smoking is less harmful than cigarette smoking. It has been shown that water-pipe use exposes smokers to substantially greater amounts of carcinogens than cigarettes. One 60-minute water-pipe smoking session is estimated to expose the user to carcinogens equivalent to as many as ten cigarettes.<sup>27</sup> Two other studies have found that water-pipe smokers are at least four times more likely to develop clinically suspicious lesions than non-smokers.<sup>28,29</sup> Given the lack of data regarding water-pipe smoking in New Zealand, research is required to estimate the actual prevalence of use of water-pipe smoking.

### Alcohol

Alcohol is another major risk factor for oral cancer. Regular and heavy alcohol drinkers have approximately two-and-a-half and five times higher risk of developing oral cancer than non-drinkers, respectively.<sup>10</sup> The effects of alcohol plus tobacco are synergistic. People who are heavy smokers and heavy drinkers are at a 48-fold risk of developing oral and pharyngeal cancers than non-smoking non-drinkers.<sup>10</sup> In New Zealand, in 2014–2015, 80% of adults drank alcohol regularly.<sup>17</sup> Among the Asian and Pacific populations of New Zealand, 56% of

**Figure 4:** A water-pipe consists of flavoured tobacco smoked through water via a pipe.



adults were regular alcohol drinkers. Of all adult New Zealanders, 18% were defined as hazardous drinkers, that is, had a drinking pattern that caused physical or mental harm to the drinkers themselves or their social circle.<sup>17</sup> People in socioeconomically disadvantaged areas are less likely to be regular alcohol drinkers, but more likely to be hazardous drinkers.<sup>17</sup> The prevalence of hazardous drinking was highest in young adults and in men, where one in four men reported hazardous drinking. A high rate of hazardous drinking was reported among the Māori and Pacific populations; close to one-third and one-fourth of these populations were hazardous drinkers, respectively.<sup>17</sup> The risk of oral and upper aero-digestive tract cancers as a result of alcohol-containing mouthwash use remains controversial. While some studies have found no association,<sup>30</sup> a systematic review has shown that alcohol-containing mouthwash users have a slightly higher risk of oral cancer than non-users.<sup>31</sup>

### Ultraviolet radiation

New Zealand has relatively high levels of ambient UV radiation (UV index 13–8 in summer) and relatively low levels of pollution.<sup>32</sup> In addition, approximately 75% of New Zealanders are of European descent with light skin tones and have a liking for the sun.<sup>32,33</sup> This, coupled with sun protection behaviour patterns, accounts for the high rate of melanoma and non-melanoma skin cancer in New Zealand.<sup>32,34</sup> While the aetiology of mucosal and skin of lip cancers is different, the lip vermilion is a bridge between the two, and is a common site for oral cancer, as it is directly exposed to UV radiation from sunlight. The magnitude of the risk for developing malignancy depends on the ambient UV radiation, which generally decreases with increasing latitude and duration of exposure determined by lifestyle.<sup>32</sup> In addition, artificial UV radiation such as those used in tanning beds pose a risk of cancer.<sup>35</sup> Although New

Zealanders do not have a higher lip to oral cavity SCC ratio than other populations, protection from UV radiation is essential to avoid lip and skin cancers.

### Human papilloma virus

High risk, or oncogenic, HPV types are those that integrate their genome into the host DNA and subsequently produce E6 and E7 oncogenes, which work to deregulate key molecules involved in the cell cycle.<sup>36,37</sup> The aetiopathogenetic role of HPV in head and neck cancers, specifically oropharyngeal carcinoma and tonsillar carcinoma, has been established. People who develop these cancers have distinct demographic features, as they particularly affect younger individuals in their third or fourth decades of life.<sup>11,13</sup> The role of HPV infection in the pathogenesis of OSCC is less certain.<sup>15,38</sup> The rate of HPV-positive OSCC has been estimated to be 1–3%, which is much lower than that of oropharyngeal SCC, in which HPV-positive SCCs contribute as much as 65%.<sup>14,15,38</sup> There are a number of methods used to detect the presence of HPV in tissues. The tumour suppressor protein p16 serves as a useful surrogate marker for significant infection by high-risk HPV and its E7 oncogene,<sup>39</sup> and can be detected on formalin-fixed specimens using immunohistochemistry (IHC). However, p16 IHC alone is insufficient to confirm the involvement of high-risk HPV.<sup>40</sup> Detection of viral oncogenes using polymerase chain reaction (PCR) of E6/E7 mRNA, quantitative PCR, or in-situ hybridisation of viral DNA or mRNA are required to confirm the role of HPV in carcinogenesis. This information is important, at least for some head and neck squamous cell carcinomas (HNSCC), since high-risk HPV-positive HNSCC, including oropharyngeal carcinoma,

is more responsive to radiotherapy, and has a better prognosis than conventional SCC.<sup>41–43</sup> It is not yet clear whether HPV status influences the prognosis of OSCC.

HPV vaccination programmes for young females have been in place in New Zealand since 2008, as well as in Australia where the programme includes both males and females.<sup>44,45</sup> The vaccination programme is to be extended to boys in New Zealand. One study reported the presence of high-risk HPV in the oral cavity of two of 219 New Zealand women.<sup>46</sup> Another study showed that 41 of 55 patients investigated had HPV-related oropharyngeal cancers.<sup>47</sup> No other data exists regarding the presence of high-risk HPV in the oral and oropharyngeal sites of New Zealanders.

## Conclusions

This paper presented an overview of the main risk factors for oral and oropharyngeal cancers and their prevalence New Zealand. Alcohol consumption is the most prevalent risk factor in New Zealand, followed by tobacco. Given the high prevalence of these two risk factors and their synergistic effect, it is important for doctors and dentists to encourage smoking cessation in smokers and to recommend judicious alcohol intake. Research is needed to determine the prevalence of use of oral preparations of tobacco and water-pipe smoking in New Zealand, especially due to changing demography and increases in migrant populations. UV radiation is also an important risk factor. Further investigations are also needed to determine the prevalence of oral and oropharyngeal cancers attributable to oncogenic HPV infection.

**Competing interests:**

Nil.

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# Individualised follow-up booklets improve recall and satisfaction for cancer patients

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## ABSTRACT

**AIMS:** The New Zealand Provisional Standards of Service Provision for Cancer recommend providing patients with written information about their diagnosis, treatment and follow up. This project aimed to develop and evaluate a resource that could be used to provide essential information to patients who were nearing completion of the surgical treatment of their cancer.

**METHODS:** The study compared patients with melanoma, colorectal and breast cancers who received standard discussion of their diagnosis, treatment and follow-up plan with cancer patients who received a discussion supported by an individualised follow-up booklet. Patients were interviewed using an over-the-phone questionnaire to assess their free recall and prompted recall of follow-up items, their perception of the level of information received and satisfaction with the communication of their follow-up plan.

**RESULTS:** The group who received a booklet as part of discussion of their follow-up plan scored significantly higher on measures of free recall, prompted recall, satisfaction with the level of information provided and overall satisfaction than those who had a standard clinic discussion but did not receive a booklet. Free recall of two relevant items improved from 61% of patients to 91%. Prompted recall of at least one item improved from 77% of patients to 100%. The proportion of patients feeling they did not receive enough information fell from 25% to 5%. The proportion of patients scoring their satisfaction at >8/10 increased from 68% to 87%. All of these measures reached significance.

**CONCLUSION:** Individualised cancer follow-up booklets are a simple, low-cost and low-risk initiative that used in a New Zealand setting, was associated with improved patient recall and satisfaction with the follow-up information they received. This supports the benefit of providing participants with personalised written information, as recommended in the New Zealand Provisional Standards of Service Provision for Cancer.

Improvements in diagnosis and treatment for breast, colorectal and melanoma cancers have led to a substantial increase in the number of people requiring post-treatment follow-up care.<sup>1,2</sup> A systematic review showed that written follow-up care plans improve patients' satisfaction and perceived knowledge of their specific follow-up.<sup>3</sup> The 2005 Institute of Medicine report issued a recommendation to provide written follow-up information as part of the follow-up plan.<sup>4</sup>

Tumour-specific service standards ensure patients receive timely, good quality care along the cancer pathway.<sup>5</sup> Provisional Standards of Service Provision for Cancer have been introduced for cancers affecting New Zealanders, including breast, colorectal

and melanoma.<sup>6,7,8</sup> For these cancers there are guidelines<sup>9,10,11</sup> regarding follow-up that include clinical review as well as surveillance investigations, such as imaging, blood tests and endoscopy. Other non-clinical follow-up recommendations are made, including the need for lifestyle advice and psychosocial support. The Provisional Standards of Service Provision for Cancer recommend that a follow-up plan is made and written information regarding this be given to each patient.<sup>6,7,8</sup> Communication between hospital specialists, the patient/whānau and general practitioner is emphasised.

This project set out to develop and evaluate a resource that could be used to provide essential information to patients who had completed or nearly completed

the surgical treatment of their cancer. The aim was to provide written information to the patient regarding their individual cancer diagnosis, the treatment they had and follow-up recommended. The booklets also included information on prognosis, symptoms to report to their general practitioner and where to get help if needed. Each booklet followed a similar structure, with differences based on the characteristics of the specific cancer. The booklets were eight A5 pages long, and aimed to provide relevant detail without being overwhelming for either patients or the clinicians using them. The booklets can be shared with support people and could assist the primary care team. By using a structured booklet, it was hoped that consistency between clinicians would be improved while still allowing for personalisation of the plans to the individual patient's circumstance. Examples of the booklets are available: Colorectal (bowel) cancer, Breast cancer, Melanoma.

## Methods

Follow-up booklets for breast, colorectal and melanoma cancers were created. These utilised fill-in-the-blanks and tick boxes, so that the booklet could quickly be individualised to the patient. The aim of this study was to evaluate the follow-up booklets' usefulness for cancer patients after their surgical treatment at a peripheral hospital, using measures of recall and satisfaction.

Participants were drawn from the Whanganui District Health Board (WDHB) catchment population of 62,210.<sup>12</sup> Individuals who were treated for a new diagnosis of breast, colorectal or melanoma cancers by the General Surgical Department at WDHB between October 2014 and December 2015 were eligible for inclusion. Eligible patients were identified using UCD codes, and from the register maintained by the Cancer Nurse Coordinator.

The WDHB Clinical Governance Committee and the Hauora Māori team were consulted, and ethical approval was received.

There was no age, gender, ethnicity or cancer staging exclusion criteria, and patients were not excluded if they had previously had a cancer diagnosis. Before contacting participants, clinic notes were reviewed to confirm the diagnosis. Participants were excluded if they suffered

advanced dementia where phone contact was thought likely to cause confusion or distress. Patients who had a mild cognitive deficit were included.

The study aimed to detect a clinically significant difference in a set of categorical variables, aiming to detect a large effect size, set at 25%. A power calculation was done to determine the number of participants needed to detect this effect size with 80% power at a 0.05 significance level for a binary variable (eg yes/no). To detect an improvement from 60% to 85%, 47 participants were needed in each group.

Group A was initially composed of patients who received a new cancer diagnosis between October 2014 and May 2015. These patients received usual information regarding follow-up at either their first post-surgery clinic or upon discharge from hospital, according to their treating surgeon's usual practice.

Group B included those who received a new cancer diagnosis between June 2015 when the booklets were approved for use, and December 2015. These patients received the new cancer-specific follow-up booklet, which was discussed with them by their surgeon at either their first post-surgery clinic or upon discharge from hospital. The booklets were developed with the input of the surgeons as well as consultation with consumers, and were provided for use by means of a display in outpatient clinic. The surgeons were encouraged to use the booklets to complement their usual practice, but this was non-mandatory. Offering the booklets was at the discretion of the treating surgeon, and was considered a part of the routine clinical follow-up consultation.

During the reconciliation process for Group B, it was unexpectedly identified that there were 20 patients who were diagnosed in the Group B inclusion period, but did not receive the follow-up booklet. These patients were offered the opportunity to participate in Group A instead. The reasons that these patients did not receive a booklet were not known.

Each participant was contacted by phone, the study explained and consent sought to proceed with the verbal questionnaire. After receiving verbal consent, a structured questionnaire was completed. The questionnaire consisted of questions designed

to evaluate patient recall and satisfaction with the follow-up process. The questionnaire had been piloted with laypeople to check for comprehension. Two interviewers were used, both receiving the same training by the same researcher. The interviewers were non-clinical hospital staff not involved in the care of the patients. The first interviewer contacted patients in Group A. The second interviewer contacted patients in Group B. It was not possible to standardise the time-lag between diagnosis and interview, as all phone interviews were conducted over a three-month period. The lag-times for Group A were longer than for Group B, with the minimum lag-time being two weeks and maximum one year. At least two attempts were made to contact patients, including one after-hours call.

To assess free recall, patients were asked to recall as many aspects of their follow-up plan as possible. Patients' responses were classified as "Two or more" if they could recall two or more relevant items about their follow-up and classified as "One or less" if they could only recall one or no aspects of their follow-up plan. This question was asked before the prompted recall question and set a high standard for recall.

To assess prompted recall, patients were asked if they remembered being told two cancer-specific items regarding follow-up. For each cancer type these included one "scheduled monitoring" item (CEA monitoring, yearly mammography, regular skin checks) and one "report to GP" item (rectal bleeding, new breast lump, changing moles). Participants that reported that they recalled being told either one or both cancer-specific follow-up items were classified as "Some Recall". If they did not recall being told about either of the follow-up items then they were classified as "None". This question set a low standard for recall.

Patients were asked to grade the information they received regarding follow-up as "Too Much", "Just Right" or "Not Enough". Patients subjectively allocated themselves into one of these categories indicating their perception of whether the level of information they received was appropriate for them.

Patients were asked to rate their satisfaction with the communication of their

follow-up plan on a scale of 1–10, with 1 being very unsatisfied and 10 being very satisfied. It was made clear that this rating should be about the follow-up process and not the overall experience they had during their time in hospital. Due to the small numbers reporting some lower scores, the results were combined into three categories (4 and under, 5–7 and over 8) to facilitate analysis.

All patients contacted who had not received a booklet in-clinic were offered the option of receiving a booklet by mail, completed as far as possible from information derived from the notes.

Demographic data and results from the phone questionnaires were recorded in an Excel spreadsheet and analysed. The Student's t-test was used to compare mean ages, and  $\chi^2$  analysis used to compare categorical variables.

## Results

For Group A, 93% (69/74) of eligible patients participated. This included the 20 patients who were re-allocated to Group A from the Group B inclusion period, all of whom participated. One breast patient was excluded due to advanced dementia, one colorectal patient was excluded due to the diagnosis of cancer being unconfirmed, two breast patients were not contactable and one melanoma patient declined consent. For Group B, 56/59 (95%) of eligible patients who had received a booklet participated. Two breast patients and one melanoma patient were not contactable. There were no patient deaths prior to contact in either group.

Demographic data showed some differences between the groups, with Group A being younger and including a higher proportion of patients with breast cancer. These differences did not reach statistical significance (Table 1). The patients who were not offered a booklet during the booklet trial period and were subsequently included in Group A included 8/20 with breast cancer, 5/20 with melanoma and 7/20 with colorectal cancer, which approximated the proportion distribution for Group B.

Free recall of the requirements of follow-up for their cancer was significantly improved in Group B participants who received the booklet at surgical follow-up

**Table 1:** Demographics for patients in each group.

Item	Group A no booklet		Group B booklet		P
	n	%	n	%	
Female	50	72%	33	59%	
Male	19	28%	23	41%	0.11
Māori	4	6%	4	7%	
Non-Māori	65	94%	52	93%	0.76
Colorectal	23	33%	25	45%	
Melanoma	13	19%	14	25%	
Breast	33	48%	17	30%	0.14
Mean age (years)	62.8		66.6		0.14
Age range	32–89		36–92		

compared to Group A participants (Table 2). In particular, the proportion of participants only able to recall “One or less” requirement was markedly reduced in Group B.

When a lower standard of recall was applied using a prompted recall approach, Group B again demonstrated a significantly greater level of recall, with 100% of the

group being able to recognise one or both of the cancer-specific follow-up facts presented.

Perception of the appropriateness of the level of information received was significantly influenced by the provision of the booklet, with very few of Group B participants reporting “Not enough” information compared to Group A participants (Table 2).

**Table 2:** Proportion of patients in each category for free recall, prompted recall, level of information and satisfaction ratings.

Item	Group A no booklet		Group B booklet		p
	n	%	n	%	
Free recall					
Two or more	42	61%	51	91%	
One or less	27	39%	5	9%	0.0001
Prompted recall					
Some recall	53	77%	56	100%	
None	16	23%	0	0%	0.0001
Level of information					
Too much	4	6%	3	5%	
Just right	48	70%	50	89%	
Not enough	17	25%	3	5%	0.01
Satisfaction ratings					
4 or less	9	13%	1	2%	
5–7	13	19%	6	11%	
8 or more	47	68%	49	87%	0.02

This was reflected in the patient satisfaction scores, with Group B having more high ratings and less low ratings than Group A.

Of the patients who were offered a booklet to be sent in the mail, 62/69 (90%) accepted one.

## Discussion

The implementation of the new cancer follow-up booklets in-clinic was associated with a significant improvement in patient recall of follow-up items in comparison to those who did not receive the booklet. A statistically significant improvement was noted in measurements of participant satisfaction. In particular, low satisfaction ratings and the number of patients who felt they did not receive enough information was substantially reduced, with corresponding increases in high satisfaction scores and patients feeling their information was just right. The detection of this effect with a relatively small sample size shows that the impact of the booklets was substantial.

These results are similar to Kenzik et al (2016) who found the use of written treatment plans in conjunction with clinician explanation was effective in increasing patient recall and long-term self-efficacy.<sup>13</sup> Kenzik et al emphasised the need for good verbal communication to reinforce written information, in particular for older cancer survivors.<sup>13</sup>

Given that providing written information is considered good practice, randomising patients to not receive a booklet when one was available was considered inappropriate, and so the retrospective cohort was used as a comparison. This created a lag-time difference between diagnosis and phone interview for the two groups, which could have affected recall due to a recency effect for Group B. The use of two interviewers could have also created bias if there were slight differences in interviewer style.

There were other demographic differences between the groups, specifically Group A was on average younger and contained more breast cancer patients than Group B, although this did not reach significance. The reasons for this are not known. This difference could have introduced bias however, if breast cancer patients differed in their recall and satisfaction compared to

melanoma and colorectal patients. Further research may be useful in this area.

The individualised follow-up booklets are a low-risk intervention that can be implemented as an integrated part of the follow-up process. It is not intended as a replacement for discussion between the patient and surgeon, but rather as a tool to complement current practice and support effective communication. Providing a written tool within a department may also help ensure consistency by encouraging adherence to local practice guidelines, especially for non-permanent clinicians such as locums and registrars. It is possible that use of the booklets modified surgeon behaviour by providing prompts on information items to discuss. It is likely that the reasons for the improvement in recall and satisfaction associated with provision of the booklets are multi-factorial.

Not all patients who were eligible to receive a booklet did, with 20/79 (25%) not being given one. Given the overall positive impact of the booklets it would be useful to understand the reasons for this. An area for future study could be to investigate barriers to provision of the booklets and how those could be rectified so that clinicians have no hesitation in providing them. In order for the booklets to be used consistently, they need to be simple and quick for surgeons, oncologists or nurses to complete, as clinic time can be limited. After surgeon feedback, the structure was adapted to make it more user-friendly. It is reassuring that all of the small number of Māori or Pacific Island patients in the study did receive booklets.

There is the potential for the development of an electronic version of the booklet with an interactive component, possibly as part of an existing system such as Patient Portals. Advantages of an electronic-based record include being easy to access, able to be updated if guidelines change and able to set alerts to remind patients to have their checkups. As the population that routinely uses technology ages, this is likely to become a more important method of providing information. Even now, many older people are able to use electronic devices, or have the support of a person who can.

There are some drawbacks with this study. The small catchment area means that there are small numbers of subgroups such as

Māori patients, limiting the possibilities for subgroup analysis. The study looked at a relatively short time period after diagnosis. Conclusions cannot be drawn with regard to impact on longer-term follow-up, adherence to the plan or clinical outcomes. Improved adherence to follow-up items was not able to be measured due to the short time frame. There is the potential for research assessing how follow-up booklets could affect long-term follow-up outcomes over five years. It is recognised that the two study groups differed in the time between their treatment and the study interview, which could have potentially contributed to differences in recall.

The booklet templates are currently available for other DHBs to modify for their own local needs. While there is a benefit to being able to localise the booklet for individual DHB conditions and resources (for

example, if a nurse specialist is available) there would also be advantages to having a suggested solution provided centrally, eg in association with the New Zealand Provisional Standards of Service Provision for Cancer. A suggested solution would help ensure consistency of resource provision throughout the country and allow DHBs to feel confident that their follow-up schedule meets the requirements of the New Zealand Provisional Standards of Service Provision for Cancer. A central approach would also help with provision of culturally specific resources, such as a Te Reo version.

Individualised cancer follow-up booklets were associated with improved patient recall and satisfaction with the follow-up process for three important cancers. We believe there is potential for developing equivalent plans for other cancer streams, for example urological or gynaecological cancers.

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Dr Lill reports grants from Ministry of Health - Faster Cancer Treatment Round Two Innovation Funding, during the conduct of the study.

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# Body mass index (BMI): association with clinicopathological factors and outcome of women with newly diagnosed breast cancer in New Zealand

Bridget Robinson, Margaret Currie, Elisabeth Phillips, Gabi Dachs, Matthew Strother, Helen Morrin, Val Davey, Chris Frampton

## ABSTRACT

**AIMS:** To identify associations of obesity with breast cancer and its outcome in a New Zealand population, including those treated with adjuvant chemotherapy.

**METHODS:** Data was collated from four regional Breast Cancer Registers, Auckland, Waikato, Wellington and Christchurch, for all women with newly diagnosed breast cancer, with weight and height recorded. Associations of body mass index (BMI) with patient and tumour characteristics, and all-cause mortality were determined.

**RESULTS:** BMI was available for 5,458 new breast cancers, 27% of all registered. BMI was normal (18.5–24.9kg/m<sup>2</sup>) for 32.7%, overweight (25–29.9kg/m<sup>2</sup>) 31.1%, obese (>30kg/m<sup>2</sup>) 34.9% and 1.3% underweight (<18.5kg/m<sup>2</sup>). Median age was 55 years. Higher BMI was associated with non-European ethnicity, post-menopausal status, screen-detection, older age and tumours with higher grade, greater size and positive progesterone receptors. Mean survival for women younger than 56 years was 18.0 years for normal BMI and 14.8 years for BMI >35 (p=0.055, Log-rank). Women younger than 56 years treated with adjuvant chemotherapy had lower survival if obese compared with normal BMI (p=0.055, Log-rank).

**CONCLUSIONS:** High BMI was associated with larger tumours, of higher grade, progesterone receptor positive and post-menopausal status. Obese pre-menopausal women treated with adjuvant chemotherapy had a trend to poorer outcome.

Obesity is increasing in the New Zealand population, with nearly two-thirds of New Zealand women overweight or obese.<sup>1</sup> Evidence is strengthening that obesity is not only associated with increased risk of developing breast cancer, but also with a poorer outcome once diagnosed.<sup>2,3</sup> Reports of poorer outcomes in obese women are inconsistent, and some suggest an association with menopausal status and breast cancer subtype.<sup>4,5</sup> Review of the International Breast Cancer Study Group adjuvant chemotherapy trials shows a poorer outcome for pre- or peri-menopausal obese women.<sup>6</sup>

Explanations proposed for the poor outcome associated with obesity have included inadequate dosing of chemotherapy, effects of the metabolic syndrome and inflammation associated with adipose tissue.<sup>7</sup> In addition, both exercise and weight loss reduce estrogen levels.<sup>8,9</sup> Thus, reduction of obesity and exercise are promoted as ways to improve breast cancer outcome, with their relative contributions yet to be clarified.<sup>10</sup> Our laboratory studies have shown that cancer-associated adipocytes, known as CAAs,<sup>11</sup> co-cultured with triple negative or estrogen receptor-positive breast cancer cell lines protect the cancer

cells from two common chemotherapy drugs used for breast cancer (Phillips, Currie, unpublished). Metformin (a drug widely used to treat obesity-related type 2 diabetes) prevented this chemotherapy resistance at clinically relevant concentrations.

The overall aim of our study was to understand the prevalence of obesity in New Zealand women with breast cancer, and to discover any associations with clinical or tumour characteristics, and whether there was any impact on outcome in a population-based patient group. Specifically, we also determined the effect of obesity on outcomes after adjuvant chemotherapy. The study used the four Breast Cancer Registers in New Zealand, which record all new breast cancers diagnosed in their region, an estimated 55% of national diagnoses in 2013.<sup>12</sup>

## Methods

### Patients

The four regional Breast Cancer Registers in New Zealand were searched for women who had body weight and height recorded at the time of their first diagnosis of a breast cancer, enabling calculation of body mass index (BMI). The register in Auckland has been entering patients for 15 years, Waikato 10 years, Christchurch six years and Wellington five years. Eligible patients were those recorded in the registers with a tissue diagnosis date for their first breast cancer prior to 31 December 2014, to enable at least one year follow-up. Recording of height and weight has been more frequent in the last five years. Where menopausal status was not known, women older than 55 years at diagnosis were recorded in the registers as post-menopausal.

### Treatment

Women were managed in their regional centre, according to nationally accepted guidelines, with routine imaging by bilateral mammography, ultrasound if needed, and magnetic resonance imaging (MRI) of the breasts when indicated. Over the study period, sentinel node biopsy gradually became the standard for T1 (less than 2cm) and small T2 tumours, with earlier patients having level 1 and 2 axillary dissection. Patients with risk factors for local recurrence after mastectomy and those having breast conservation were referred to the regional radiation oncology service, and those with risk factors for distant spread

were referred to the regional medical oncology service to consider systemic adjuvant therapies. Patients with locally advanced disease received neoadjuvant systemic therapy, prior to surgery and radiation. Standard adjuvant chemotherapy regimens were based on anthracyclines and taxanes, following international guidelines. Women with human epidermal growth factor receptor-2 (HER2) positive tumours received trastuzumab with chemotherapy when chemotherapy was indicated. Women with estrogen receptor (ER) positive tumours were offered adjuvant endocrine therapy, following international guidelines. Reconstructive surgery was performed either at the initial operation or some years later. Women with more than four nodes involved, locally advanced primary tumours, or suspicious symptoms or signs underwent staging with blood tests (blood count, liver and renal function, including calcium), computerised tomography (CT) scan of chest, abdomen, pelvis and bone scan. Other imaging was undertaken when indicated clinically. Positron emission tomography-computerised tomography (PET-CT) scan imaging using fluoro-deoxy glucose (FDG) or sodium fluoride (NaF) is not yet funded in the New Zealand public health service so was rarely used. In all centres regular multidisciplinary meetings review staging and pathology, and make management decisions.

### Statistics

The demographic details, age, breast cancer type and stage, estrogen, progesterone and HER2 receptor status, treatment and outcome were collated from the registers. The WHO definitions<sup>13</sup> were used to group BMI, with normal BMI defined as 18.5–24.9kg/m<sup>2</sup>, overweight 25–29.9kg/m<sup>2</sup>, with obese level 1 defined as 30–34.9kg/m<sup>2</sup>, obese level 2 as 35–39.9kg/m<sup>2</sup>, obese level 3 as >39.9kg/m<sup>2</sup>, and underweight as <18.5kg/m<sup>2</sup>. Ethnicity was self-reported and followed the New Zealand census definition. Post-menopausal status was taken as aged older than 55 years when not known. The associations between patient and tumour factors and BMI group were determined using Pearson's correlation coefficients and one-way ANOVA as appropriate. Factors showing significant univariate associations with BMI were then entered into a general linear model with BMI as the dependent variable to determine the significant independent associations with BMI. All-cause

mortality was determined for the entire group of women. After excluding patients with more than one breast cancer, and those with metastases at presentation, the associations between BMI, age group, menopausal status, nodal status, tumour T stage, receptor status and chemotherapy usage and all-cause mortality were analysed using Log-rank tests and Cox proportional hazards regression models, and using Kaplan Meier curves. The outcome for women who received adjuvant chemotherapy was explored by BMI and menopausal status.

### Ethics

The registers themselves are approved by the regional Health and Disability Committees, including approval from their regional Health and Disability Ethics Committee to release de-identified data of patients on the registry databases, and this study was approved by the University of Otago Ethics Committee (12/319).

## Results

### Clinicopathological factors

There were 5,458 new breast cancers diagnosed in women with BMI recorded from the four regional registers (comprising 27% of the total 20,056 registrations in the four registers), 1,261 from Auckland (10% of registrations), 4,787 from Waikato (57% of registrations), 464 from Wellington (32% of registrations), 1,009 from Christchurch (55% of registrations). The Auckland register has operated for the longest period of time, and had the lowest proportion of women with height and weight recorded. The patient demographic and clinicopathological data at diagnosis for these 5,458 tumours are shown in Table 1. Approximately one-third were of normal BMI (18.5–24.9kg/m<sup>2</sup>), one third overweight (25.0–29.9kg/m<sup>2</sup>) and one-third obese (BMI>30kg/m<sup>2</sup>). The median age was 55 years. The majority (77.4%) were New Zealand European ethnicity, 13.4% New Zealand Māori, 5.2% Asian, 3.4% Pacific Island and 0.6% other.

**Table 1:** Clinicopathological characteristics at diagnosis for all breast cancers in women who had BMI recorded at diagnosis (number of cancers=5,458).

Characteristic	Subgroup	Number	Percent of total
Total		5,458	100
BMI, kg/m <sup>2</sup>	<18.5 underweight	73	1.3
	18.5–24.9 normal	1,785	32.7
	25–29.0 overweight	1,697	31.1
	30–34.9 obese 1	1,074	19.7
	35–39.9 obese 2	487	8.9
	40 + obese 3	342	6.3
Ethnicity	European	4,217	77.5
	Māori	727	13.4
	Asian	281	5.2
	Pacific	185	3.4
	Unknown	33	0.6
Presentation of cancer	Screening	1,881	34.5
	Symptomatic	3,558	65.2
	Unknown	19	0.3
Age at diagnosis	<40 years	486	8.9
	40–49 years	1,402	25.7

**Table 1:** Clinicopathological characteristics at diagnosis for all breast cancers in women who had BMI recorded at diagnosis (number of cancers=5,458) (Continued).

	50–59 years	1,546	28.4
	60–69 years	1,154	21.1
	70–79 years	574	10.5
	>79 years	294	5.4
Menopausal status	Post-menopausal	3,102	56.7
	Pre/peri-menopausal	2,356	43.1
Tumour histology	Ductal	4,432	81.2
	Lobular	564	10.3
	Other, unknown	462	8.5
Tumour grade	Low	834	15.3
	Intermediate	2,424	44.4
	High	1,959	35.9
	Unknown	241	4.4
Tumour stage	T1 (<20mm)	2,490	45.6
	T2 (20–49mm)	2,232	40.8
	T3, T4 (>49mm, locally advanced)	690	12.5
	Unknown	46	0.1
Tumour estrogen receptor	Positive	4,163	76.3
	Negative	1,189	21.8
	Unknown	106	1.9
Tumour progesterone receptor	Positive	3,392	62.1
	Negative	1,919	35.2
	Unknown	147	2.7
Tumour HER2 status	Positive	1,038	19.0
	Negative	3,397	62.2
	Unknown	1,023	18.8
Tumour triple negative		548	10.0
Nodal status, axilla	Positive	2,496	45.8
	Negative	2,621	48.0
	Unknown	341	6.2
Vascular/lymphatic invasion	Present	1,633	29.9
	Absent	3,765	69.0
	Unknown	60	1.1
Metastases at diagnosis	Present	285	5.2
	Not detected	1,801	33.0
	Staging not indicated	3,372	61.8
	Unknown	16	0.2

**Table 2:** Associations of BMI with patient demographic factors and tumour characteristics, univariate analyses. P-values are derived from Pearson's correlation coefficients and ANOVA.

Characteristic	Number in analysis	P value
Ethnicity	5,443	<b>&lt;0.001</b>
Age at diagnosis	5,458	<b>0.015</b>
Menopausal status	5,458	<b>0.024</b>
Screening vs symptomatic	5,439	<b>&lt;0.001</b>
Histology type	5,427	0.815
Tumour size	5,192	<b>&lt;0.001</b>
Tumour grade	5,217	0.035
Estrogen receptor	5,352	0.365
Progesterone receptor	5,311	<b>&lt;0.001</b>
HER2 status	4,435	0.26
Number positive nodes	5,117	0.133
Distant metastases	2,086	0.195

### Associations with high BMI

Univariate analysis (Table 2) showed that higher BMI was significantly associated with non-European ethnicity, post-menopausal status, detection by screening rather than presenting with symptoms, increasing age at diagnosis, as well as positive progesterone receptor on the tumour, higher grade and larger tumour size (p values less than 0.05 were regarded significant). On multivariate analysis, all these factors remained independently associated with BMI in the general linear model with the exception of age (data not shown).

### Outcome by BMI

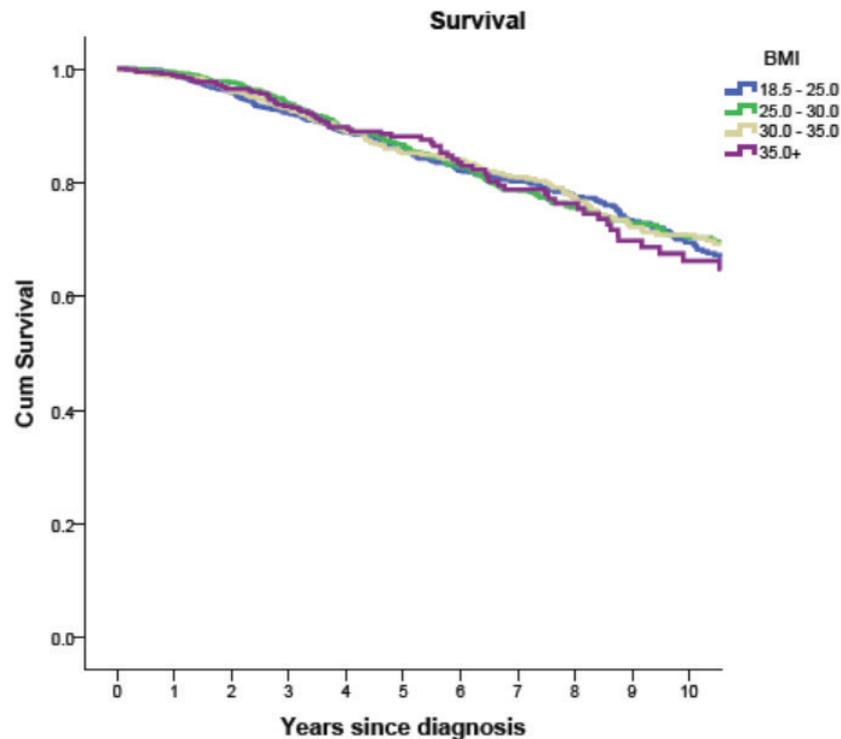
All-cause mortality was analysed as the primary endpoint by Kaplan Meier method for the 5,150 women with a single primary cancer, by BMI group. Women with more than one primary cancer were excluded since survival could relate to either cancer. The normal, overweight and obese BMI groups each had a similar mean overall survival, 16 years, with median follow-up 3.2 years. Median survival was not reached. The underweight BMI group had a significantly poorer survival, with median and mean both eight years. The underweight women made up 1.3% of the whole group, and included 12.0% with metastatic disease,

compared with 5.1% for normal or high BMI. Women with BMI less than the lower limit of normal were excluded from subsequent survival analyses, since low weight is associated with poorer outcome<sup>2,14</sup> due to inclusion of more women with metastatic disease or comorbidities. The Kaplan Meier survival curves by BMI, once women with metastases and BMI less than 18.5kg/m<sup>2</sup> were excluded, showed no distinguishable effect of raised BMI, with median follow-up of 3.2 years (Figure 1).

### Age and menopausal status

The possible effect of age on impact of BMI on survival was explored, initially using all women with a single primary tumour, and excluding those with lower than normal BMI, shown in Figure 2. The cut-off using age 55 years or less, or older than 55 years was selected since 55 years was the median age, and also served as a surrogate for menopause. For women of 55 years of age or younger, mean survival was 17.0 years and decreased with higher BMI (18.0 years for normal BMI, 16.1 years for BMI 25–29.9kg/m<sup>2</sup>, 16.3 years for BMI 30–34.9kg/m<sup>2</sup>, and 14.8 years for BMI greater than 35kg/m<sup>2</sup>, Log rank-test p=0.055; p<0.05 for significance). The women older than 55 years had mean survival of 13.7 years, and

**Figure 1:** Cumulative Survival (all-cause mortality), according to BMI as kg/m<sup>2</sup>, for all women with a single primary breast cancer, after excluding those with metastases and those with BMI less than 18.5kg/m<sup>2</sup>. Number of women is 1,601 for BMI 18.5–224.9kg/m<sup>2</sup>, 1,538 for 25.0–29.9kg/m<sup>2</sup>, 962 for 30.0–34.9kg/m<sup>2</sup>, and 721 for >34.9kg/m<sup>2</sup>.



this trended towards being longer at higher BMI ( $p=0.065$ , Log-rank test). For these older women, the mean all cause survivals were 12.3 years for normal BMI, 13.3 years for 25–29.9kg/m<sup>2</sup>, 14.9 years for 30–34.9kg/m<sup>2</sup> and 14.2 years for BMI greater than 35kg/m<sup>2</sup>. Thus, increased BMI had a non-significant adverse effect for younger women, and was potentially favourable for older women. The hazard rate for survival for women with BMI greater than 35kg/m<sup>2</sup> was significantly more favourable for those aged over 55 years ( $HR=0.72$ ) compared with those aged less than 56 years ( $HR=1.40$ ). Overall however, the effect of BMI on survival outcome and age did not reach significance ( $p=0.075$ ).

### Pathological prognostic factors

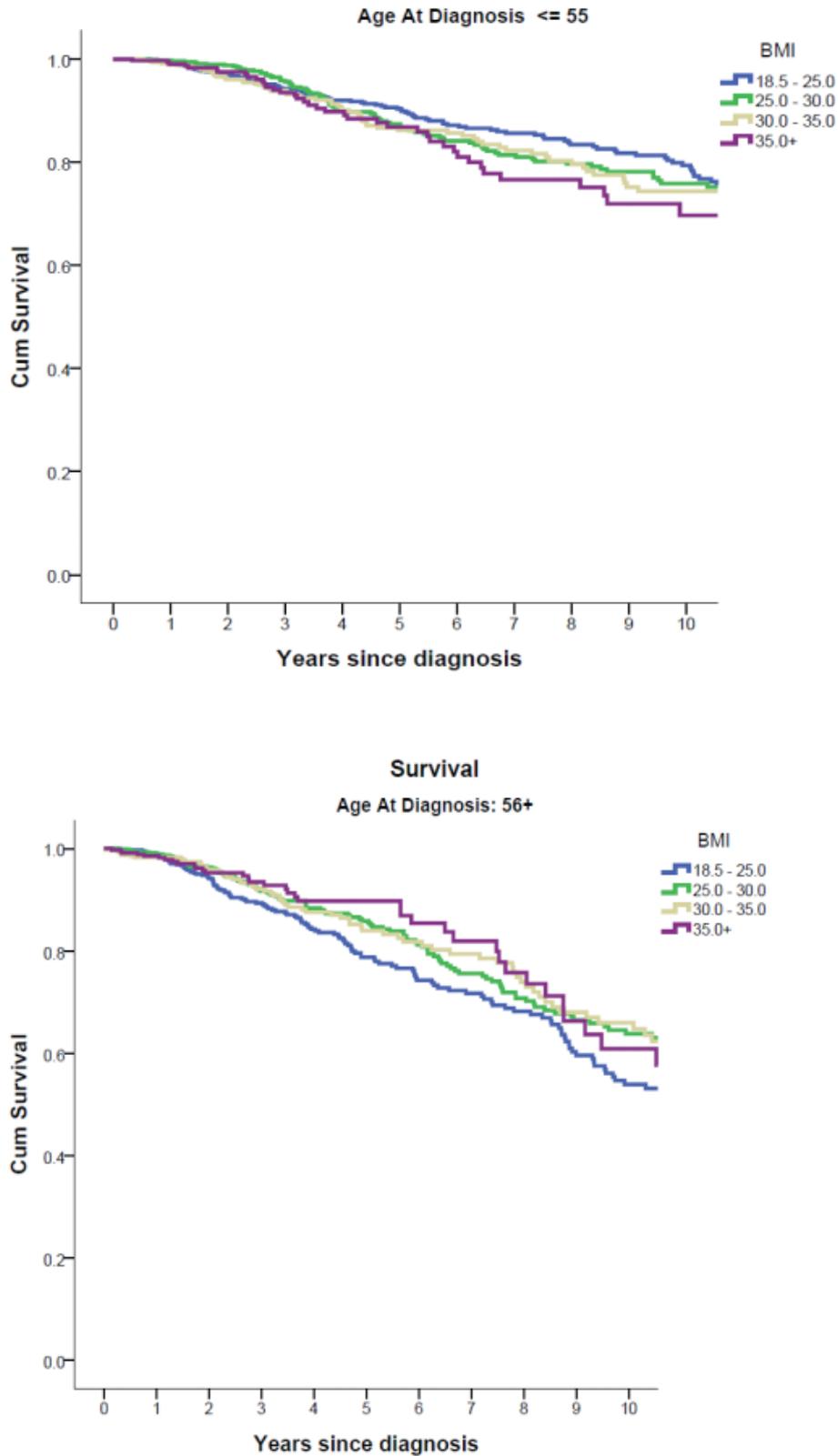
Tumour and nodal features, which impact on outcome, were further explored with respect to interaction with BMI. Outcome by nodal status, for all ages, by BMI was determined, with mean survival 17.1 years for women with node-negative cancers ( $n=2,401$ ), and 14.5 years for node-positive cancers ( $n=2,247$ ). As expected, the effect of nodal status on survival was highly significant ( $HR=1.40$ ,  $p<0.001$ ). There were no

significant effects on survival by BMI group according to nodal status, but the group with BMI greater than 35kg/m<sup>2</sup> tended to do better than normal weight if node-negative, and were trending to worse outcome than normal weight after five years when node-positive (data not shown). Tumour size or T stage had the expected effect on survival overall, but there was no effect by BMI group (data not shown). The expected higher prevalence of ER positive tumours at older age was seen, with 81.1% for age greater than 55 years, and 77.3% for younger women, but there was no significant variation in ER positivity by BMI and age greater than or less than 55 years, either for the whole group or just those receiving adjuvant chemotherapy.

### Adjuvant chemotherapy

The number of women receiving adjuvant chemotherapy according to BMI status was explored. The women with metastatic disease at diagnosis were excluded along with those with more than one primary cancer, leaving 4,888 women with early disease for whom chemotherapy would be considered. The use of chemotherapy was similar for the normal (57.5% of women),

**Figure 2:** Cumulative Survival (all-cause mortality) for normal, overweight and obese BMI groups, according to age, greater or less than 55 years.



Includes 2,583 women 55 years of age or younger (top figure), and 2,239 older than 55 years (bottom figure), all with one breast cancer; excludes the lowest BMI group (less than 18.5kg/m<sup>2</sup>). For 55 years and younger, number of women is 922 for BMI 18.5–24.9kg/m<sup>2</sup>, 809 for BMI 25.0–29.9kg/m<sup>2</sup>, 491 for BMI 30.0–34.9kg/m<sup>2</sup>, and 361 for BMI >34.9kg/m<sup>2</sup>. For older than 55 years, number of women is 679 for BMI 18.5–24.9kg/m<sup>2</sup>, 729 for BMI 25.0–29.9kg/m<sup>2</sup>, 471 for BMI 30.0–34.9kg/m<sup>2</sup> and 360 for BMI >34.9kg/m<sup>2</sup>.

overweight (58.1%) and high BMI groups (59.8% for BMI 30–34.9kg/m<sup>2</sup>, 55.1% for BMI 35–39.9kg/m<sup>2</sup>, and 55.3% for BMI of 40kg/m<sup>2</sup> and higher). However, a smaller percentage (38%) of underweight women (BMI <18.5kg/m<sup>2</sup>) received chemotherapy. Since the effect of BMI on outcome may depend on menopausal status, or age greater or less than 55 years, and benefit of adjuvant chemotherapy declines with advancing age, survival (all-cause mortality) was examined for the women who were treated with chemotherapy, for those aged 55 years or younger, and those aged over 55 years, according to BMI. The BMI groups were defined for this analysis as normal and overweight combined (BMI=18.5–29.9kg/m<sup>2</sup>), BMI 30–34.9kg/m<sup>2</sup>, and BMI more than 35kg/m<sup>2</sup>. The 1,964 women under 56 years on chemotherapy showed lower survival at high BMI (p=0.055, Log Rank), while the 826 women aged over 55 years showed no association of survival with BMI. For women who did not receive chemotherapy, 618 under 56 years and 1,413 over 55 years, there was no significant effect of BMI on all-cause mortality (data not shown).

To further explore the trend to poorer survival for more obese premenopausal women treated with chemotherapy, Kaplan Meier survival (all-cause mortality) was estimated for all premenopausal women, with one cancer and no metastases (n=2,231), by BMI group. The mean survival was 21.0 years overall, 21.7 years for BMI 18.5–24.9kg/m<sup>2</sup>, 20.9 years for BMI 25–29.9kg/m<sup>2</sup>, 20.2 years for BMI 30–34.9kg/m<sup>2</sup>, 17.5 years for BMI 35–39.9kg/m<sup>2</sup> (p=0.045, compared with normal BMI, Log Rank (Mantel-Cox) by pairwise comparison) and 19.3 years for BMI of 40kg/m<sup>2</sup> or more (non-significant overall). Mean survival was determined for the cohort of premenopausal women with ER-positive tumours (n=1,704), and for the subset who had chemotherapy (n=1,181). Mean survival was 20.5 years and 20.4 years respectively, and there was no significant effect of BMI group (data not shown).

## Discussion

Two-thirds of this large cohort of women with newly diagnosed breast cancers in four regions of New Zealand were overweight (31%) or obese (35%). Higher

BMI was significantly correlated with non-European ethnicity, post-menopausal status, detection by screening rather than presenting with symptoms, positive progesterone receptor on the tumour, increasing age at diagnosis and larger tumour size. Those women who had a BMI below normal (BMI<18.5kg/m<sup>2</sup>) had significantly poorer outcome, while for women of normal, overweight or obese BMI, there was no effect of BMI on all-cause survival. Women with BMI greater than 35kg/m<sup>2</sup> had a proportionately poorer outcome if less than 56 years, compared with those older than 55 years. There was a poorer outcome for pre-menopausal women (less than 56 years of age) treated with adjuvant chemotherapy. Women with less than normal BMI were less likely to receive chemotherapy than normal weight women, while overweight and obese women had similar uptake rates to women of normal BMI.

The association of higher BMI with post-menopausal status, older age, detection by screening and larger primary tumour has been reported for other large population series.<sup>2,3,6,15</sup> The association with progesterone receptor status, separately from estrogen receptor status,<sup>16,17</sup> is hypothesised as due to its effect on peripheral aromatisation of estrogen.<sup>15</sup> While the larger primary tumour, detected by screening, might reflect more difficulty in detection in a larger breast, it could also reflect more aggressive biology, since higher grade is associated with obesity. The association of poorer outcome with increasing BMI in younger women, and with better outcome in older women, remain unexplained,<sup>14,15</sup> but supports the need for further studies into mechanisms such as estrogen metabolism, adipocyte effect on response of tumour cells to chemotherapy (Phillips, Currie, unpublished), insulin effects and inflammation.<sup>7</sup> The Breast Cancer Registers differ from the New Zealand Cancer Registry in each being dedicated to a specific region, and in recording much additional data, over and above the pathology, age and date of diagnosis. While they accrue all women diagnosed in the region, only women with height and weight recorded were included in this study, and their median age was five to ten years younger compared with national New Zealand Cancer Registry data

for the three years to 2013.<sup>18</sup> The distribution of BMI, however, closely matches that of the New Zealand female population.<sup>1</sup> The BMI group could be biased to women who needed their height and weight determined for receiving chemotherapy, or because of clinical concerns about their BMI. The clinicopathological data are similar to other patterns of care cohorts,<sup>19</sup> supported by the expected dependence of survival on axillary nodal positivity, tumour (T) stage and estrogen receptor status.

A poorer outcome on adjuvant chemotherapy has been reported on re-analysis of three large randomised clinical trials using anthracycline and taxanes (concurrent or sequential), with a poorer survival for BMI greater than 30kg/m<sup>2</sup> for the BIG-2-98 trial,<sup>20</sup> for BMI greater than 40kg/m<sup>2</sup> in the SUCCESS A trial,<sup>21</sup> and on long follow-up of ECOG E1199,<sup>22</sup> which also suggested a bigger effect for ER-positive tumours. Analysis of eight pooled trials of neoadjuvant chemotherapy showed a lower pathological complete response rate (pCR) to taxanes for high BMI.<sup>23</sup> A large meta-analysis<sup>24</sup> showed an adverse effect of increased BMI only in pre- or peri-menopausal women, and only for ER-positive tumours. In contrast, in the ADEBAR trial of sequential anthracycline and taxane, high BMI had an adverse effect on survival in post-menopausal women.<sup>25</sup> Our data, though only marginally significant, are consistent with an adverse effect of high BMI in younger women on chemotherapy, but analysis including only the ER-positive tumours did not reveal a stronger association of outcome with BMI. Strengths of this study are the relatively unselected inclusion of all women on the four registers, who had BMI determined, the overall large number of women for whom data had been collected prospectively, and that they received usual care, rather than having been eligible for a clinical trial with restrictive entry criteria. All-cause mortality is a sound end point, but may miss effects of BMI on breast cancer mortality alone. Analysis by

receipt of adjuvant chemotherapy allowed a more homogeneous group to be studied to determine more clearly any effects of BMI on outcome after chemotherapy.

Weaknesses of the study are the younger age than the contemporaneous national registry data, the currently short median follow-up at 3.2 years and lack of disease-free survival endpoints, though these are less robustly recorded in observational studies than in randomised trials. The underweight women, who made up 1.3% of the BMI group, had a mean survival half that of the other women, as seen in other cohorts.<sup>2,18</sup> A higher proportion of the underweight women had metastases, and could have included women with comorbidity, which was not collected in the registers. There was no central review of pathology, although synoptic reporting was introduced during this period, and reporting became standardised between the registers. Drug doses and dose intensity have not been explored in this study, but will be the subject of a future study. Neutropenia has been reported to be more common at low or normal BMI than at high BMI,<sup>26</sup> suggesting relative underdosing at higher BMI and/or inappropriate dose reductions. Finally, appropriate BMI cut-offs for obesity may differ for different ethnic population groups,<sup>1,13</sup> and other measures such as waist circumference may better reflect risk.<sup>13</sup>

### Implications and further research

This study shows that New Zealand women are likely to be similar to other women worldwide and that higher levels of obesity are likely to confer a poorer outcome for breast cancer, especially for younger women who receive adjuvant chemotherapy. Studies support greater benefit from combining weight loss with increased physical activity, but the specific requirements and mechanisms remain uncertain.<sup>4,8,9</sup> Both should be promoted to patients, and intervention studies continued, together with exploration of biomarkers, especially in obese women on adjuvant chemotherapy.

## Conclusion

This study confirms the high frequency of high BMI, including severe obesity in women diagnosed with breast cancer, as in the female population of New Zealand. More obese women had larger primary tumours, were less likely to present with a symptomatic lump and more likely to have their breast cancer detected by screening, and tended to be older. The outcome for pre- and peri-menopausal women when treated with adjuvant chemotherapy as

standard care tended to be poorer for those with very high BMI, offering preliminary results suggesting that real life outcomes are consistent with several recent publications from randomised clinical trials. Longer follow-up is needed together with ongoing research to uncover biomarkers for the adverse effects of high BMI, and to establish how weight loss and increased physical activity impacts on outcome. Clinicians need to record height and weight for all women with breast cancer.

### Competing interests:

Dr Davey and Dr Robinson report grants from New Zealand Breast Cancer Foundation during the conduct of the study. Dr Morrin reports grants from New Zealand Breast Cancer Foundation and the Canterbury West Coast Division of the Cancer Society of New Zealand during the conduct of the study.

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# Reducing the polyp burden in serrated polyposis by serial colonoscopy: the impact of nationally coordinated community surveillance

Susan Parry, Randall W Burt, Aung Ko Win, Ye Kyaw Aung, Sonja Woodall, Julie Arnold, Mark Clendenning, Daniel D Buchanan, Timothy J Price, Christophe Rosty, Joanne P Young

## ABSTRACT

**BACKGROUND:** Serrated polyposis syndrome (SPS) is associated with an increased risk of colorectal cancer (CRC) and an evolving management approach. The aims of this study were to assess the polyp burden reduction over time, and the incidence of CRC in serrated polyposis patients undergoing community surveillance.

**METHODS:** This is an observational study based on prospectively collected data. A total of 96 SPS patients with no personal history of CRC were prospectively enrolled in a surveillance program under the guidance of a tertiary center. Patients underwent surveillance colonoscopy in multiple centres across New Zealand.

**RESULTS:** Patients underwent a median of four colonoscopies with a median interval of 15 months over a median follow-up period of 4.8 years. Five of 96 patients (5%) were referred for surgery, and the remaining 91 were managed by colonoscopy alone. In patients referred for surgery, 92% of the surveillance intervals to the fourth colonoscopy had been  $\leq 12$  months compared to 33% ( $P < 0.001$ ) in the colonoscopy only group, and all five (100%) had  $\geq 20$  pancolonial polyps after four procedures compared with only 5/91 (5%) in those managed by colonoscopy alone. In patients successfully managed by colonoscopy, 86% had  $< 10$  pancolonial polyps,  $> 75\%$  no longer had polyps  $\geq 10$ mm and  $> 90\%$  no longer had proximal serrated polyps  $\geq 10$ mm after the fourth colonoscopy. No patients were found to develop CRC during the study time period.

**CONCLUSIONS:** Patients with SPS were managed by proactive surveillance colonoscopy in wider hospital settings under tertiary centre guidance, with only 5% requiring surgical management. No CRC was diagnosed in any patient during surveillance.

Serrated polyposis syndrome (SPS), formerly known as hyperplastic polyposis, is a disorder of unknown aetiology, characterised by the occurrence of multiple serrated polyps in the large bowel and an increased risk of colorectal cancer (CRC) for affected individuals and their relatives.<sup>1-4</sup> The prevalence of SPS in the general population is currently unknown and is thought to be underestimated.<sup>5,6</sup> There are evolving views on what is considered the optimal management for individuals with SPS. For

endoscopists undertaking colonoscopic surveillance the major concern is the reported occurrence of CRC despite the colonoscopy interval being one to two years.<sup>7</sup> It is unknown whether this represents sub-optimal control of polyp numbers, a high 'miss rate' in the proximal colon, or rapid malignant transformation of advanced serrated polyps *per se*.<sup>7-9</sup>

Current guidelines recommend that SPS patients should be offered yearly colo-

scopic surveillance with intent to clear the proximal colon of all polyps, or at a minimum all polyps  $\geq 5$ mm in size if there are numerous diminutive lesions. Surgery is advised if endoscopic control of polyps is not feasible.<sup>10</sup> However, there is limited information on the time frame and residual polyp burden that defines failed or failing endoscopic control. The aims of this study were 1) to record the polyp burden over time and the incidence of CRC in SPS patients who were participating in a community colonoscopic surveillance program with tertiary center guidance, and 2) to identify characteristics of patients who mandated prophylactic colorectal surgery as part of their management.

## Methods

### Study cohort

Patients from urban and regional areas throughout New Zealand with suspected SPS, regardless of whether there was a family history of CRC, were referred by colonoscopists (either gastroenterologists or surgeons) to the New Zealand Familial Gastrointestinal Cancer Service (NZFGICS), a national multidisciplinary tertiary service with longstanding expertise in the diagnosis and management of familial gastrointestinal polyp and cancer syndromes. Referral was made to request ongoing management recommendations regarding colonoscopy surveillance intervals or surgery in their patient with SPS and colonoscopic surveillance advice for first-degree relatives. Those with a confirmed diagnosis of SPS were prospectively offered enrolment in the Genetics of Serrated Neoplasia (GSN) study from 2000 to 2014. For inclusion in the study, patients had to meet the World Health Organization (WHO) criterion 1 (at least five histologically confirmed serrated polyps proximal to the sigmoid colon, with two or more of these being  $> 10$ mm) and/or criterion 3 ( $> 20$  serrated polyps of any size but distributed throughout the colon) for SPS,<sup>3</sup> as these two criteria are relevant to control of polyp burden.<sup>11</sup> Exclusion criteria covered patients with known or suspected Lynch syndrome, known to be *APC* or bi-allelic *MUTYH* mutation carriers, and patients with a previous history of colorectal surgery due to 1) colorectal cancer or 2) conditions other than CRC. Patients gave

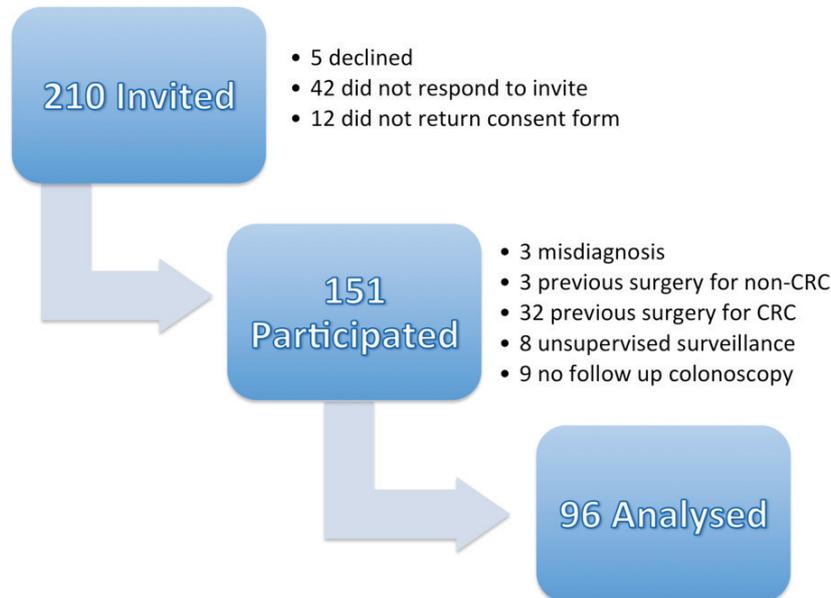
written informed consent to participate in research (HDEC of NZ Protocol NTX 08/03/013). Patients who declined participation in the study were offered identical clinical management recommendations by the tertiary service.

### Study design and data collection

The NZFGICS clinical advisors (gastroenterologists or colorectal surgeons) reviewed the colonoscopy and histology reports after each procedure, and the referring clinician and patient were given prospective management recommendations. Following the management recommendations, colonoscopies continued to be performed by the referring specialists within 31 public or private hospital endoscopy units. For a subset of the patients (27%) NZFGICS specialists performed the procedures in their hospital practice. At each surveillance procedure, the aim was to complete examination to the caecum and ensure that all visible polyps proximal to the sigmoid colon were removed with  $< 10$  polyps ( $\leq 5$ mm in size) remaining in the distal colorectum. Surveillance was recommended at 12–18 month intervals, with initial earlier repeat procedures at intervals of 12 months or less if the aims for polyp control were not being achieved, there was evidence of incomplete polyp removal or there was poor bowel preparation. Colectomy with ileo-rectal anastomosis was recommended for non-resectable large polyps and/or recurring numerous polyps. Patients who went to surgery were censored at time of surgery for the follow-up analysis.

Each colonoscopist documented the number, size and location of polyps at each procedure, and these were linked to the corresponding histology report. Polyps were classified into conventional adenomas and hyperplastic/serrated polyps. All subtypes of serrated polyps, as defined by the WHO,<sup>3</sup> were grouped as a single entity and considered by size ( $<$  or  $\geq 10$ mm) and site (proximal or distal colon). The proximal colon included the caecum, ascending colon and transverse colon. As far as possible, polyp counts were estimated from colonoscopy reports. Where reports documented ranges in polyp numbers or reported, for example greater than 20 polyps, the lower number was recorded.

**Figure 1:** Triage of patients invited to participate in the Genetics of Serrated Neoplasia study (n=210).



Fifty-nine patients did not participate (28%). Thirty-two patients (15%) had previous surgery for CRC. Previous surgery for non-CRC (n=3) describes three patients excluded from the intact colons group with no prior CRC who had undergone surgical removal of large tubulovillous adenomas or a carcinoid.

## Statistical analysis

Statistical analyses were performed with SPSS statistical software version 23.0 (IBM) and Prism V7. Comparisons were performed using a chi-squared or exact test for categorical variables and a *t*-test for continuous variables. A two-tailed *p*-value was used for comparative analyses and a *p*-value of less than 0.05 was used to determine statistical significance.

## Results

### Baseline characteristics

A total of 210 SPS patients were invited to participate, and a final 96 were initially included in the study (Figure 1). Patient characteristics are listed in Table 1. Of the participants, six (6%) met WHO criterion 1 only, 23 (24%) met both WHO criteria 1 and 3, and the remaining 70% met WHO criterion 3 only. Thirty patients (31%) in this cohort had been described in previous reports.<sup>12,13</sup>

### Colonoscopies

A total of 335 colonoscopies were reviewed (96 initial and 239 subsequent procedures). A small number of incomplete procedures for poor bowel preparation or technical reasons were not counted in the total. No patient underwent surgical treatment for complications of colonoscopy.

Patients were partitioned into those who were referred for prophylactic colectomy (n=5) and those who remained on colonoscopy surveillance (n=91). In patients referred for colectomy, only procedures prior to surgery were included in the analysis. Of all patients studied, 28 had two, 22 had three, 27 had four and 19 had five or more procedures. Surveillance characteristics for each group are presented in Table 2 and numbers of colonoscopies analysed are shown in Figure 2.

### Polyp features

The polyp features across serial procedures are illustrated in Figure 3. An average pan-colonic serrated polyp count of <10 was documented after four colonoscopies for patients who were not referred for surgery (n=91), with only 14% (13/91) of these patients having individual polyp counts of ≥10 at this procedure. In contrast, in patients who underwent prophylactic colectomy (n=5) the average pan-colonic serrated polyp count remained at 20 or greater throughout four procedures (Figure 3a). Overall, >75% of patients managed by colonoscopy no longer have polyps ≥10mm in size at the fourth colonoscopy. However, at least one polyp of any size was still present in the proximal colon in at least 80% of all patients (Figure 3b). Large (≥10mm) serrated polyps

**Table 1:** Patient details and baseline polyp features of serrated polyposis patients.

	All patients n=96	Colonoscopy surveillance n=91	Prophylactic surgery n=5	P-value *
Median age at diagnosis (IQR) years	48 (33–59)	44 (32–59)	54 (53–64)	
Patients (females)	96 (60)	91 (54)	5 (4)	0.65
Ever smoker (%)	58 (60)	54 (59)	4 (80)	0.65
Current smoker (%)	19 (20)	18 (20)	1 (20)	0.99
Family history CRC (FDR, SDR) (%)	56 (58)	53 (58)	3 (60)	0.99
First-degree family history of CRC (%)	19 (20)	18 (20)	1 (20)	0.99
WHO Criterion 3 (%)	90 (94)	85 (94)	5 (100)	0.99
Polyps >10mm (%)	61 (64)	58 (64)	3 (60)	0.99
Proximal polyps >10mm (%)	46 (48)	43 (48)	3 (60)	0.99
Serrated polyps >10mm (%)	53 (55)	50 (57)	3 (60)	0.97
Proximal serrated Polyps >10mm (%)	42 (44)	39 (43)	3 (60)	0.65
Any conventional adenoma (%)	59 (61)	55 (60)	4 (80)	0.65
Advanced adenoma# (%)	13 (14)	12 (13)	1 (20)	0.99

\* Colonoscopy only surveillance group vs prophylactic surgery.

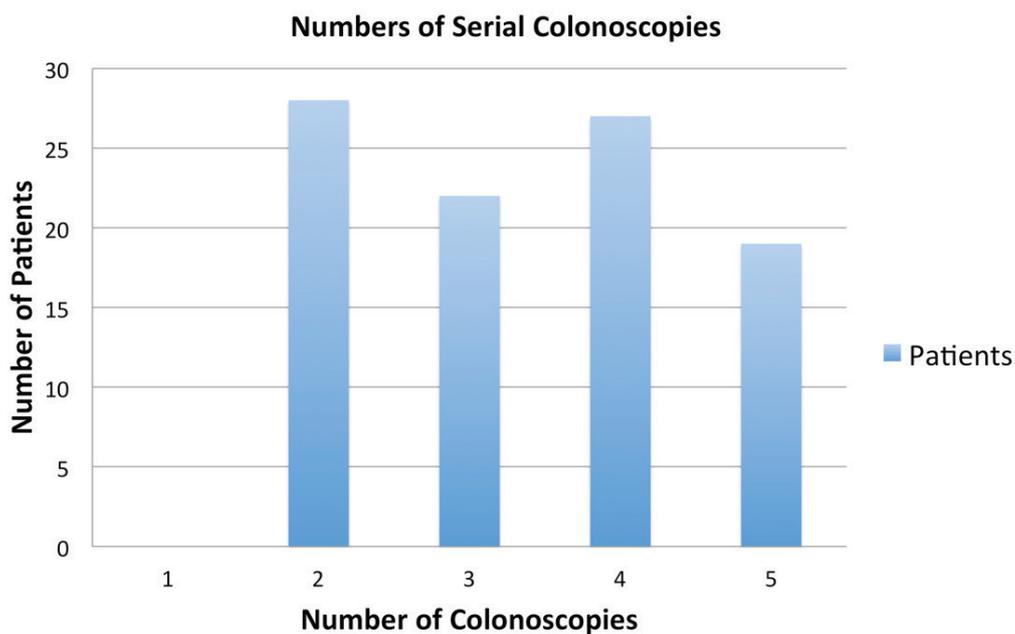
#Advanced adenoma includes those with high-grade dysplasia, villous histology and size 10mm or greater.

FDR = first-degree relative.

SDR = second degree relative.

IQR = interquartile range.

**Figure 2:** Graphical representation of numbers of patients who underwent two, three, four and five or more colonoscopies.

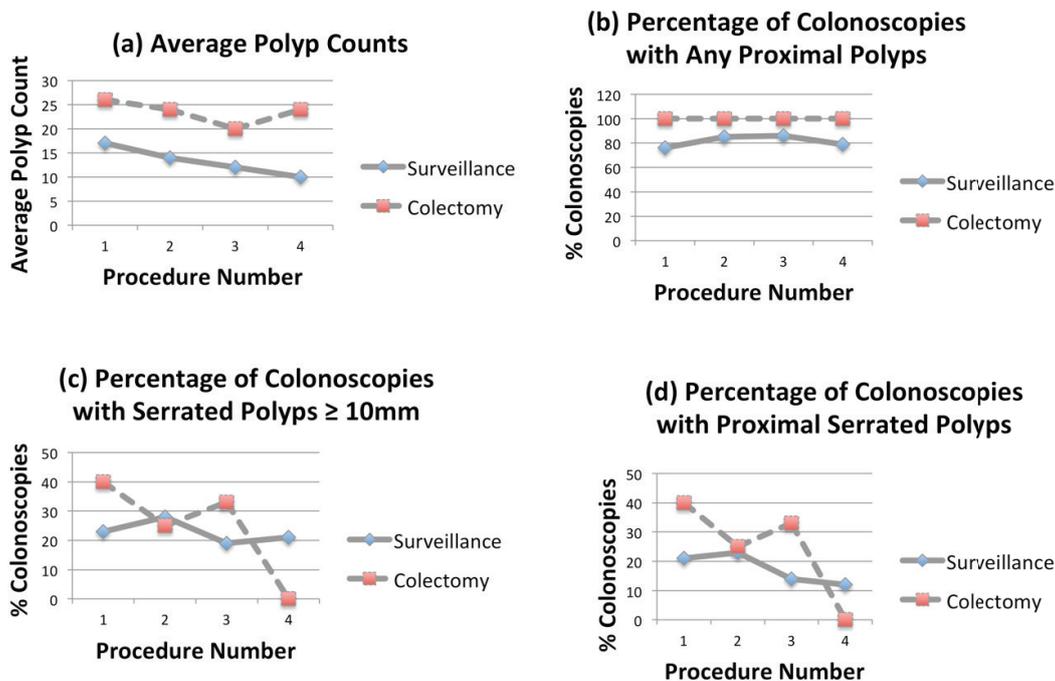


**Table 2:** Surveillance characteristics of each patient group.

	All patients	Colonoscopy surveillance	Prophylactic colectomy	P-value
Median follow-up (IQR) years	3.6 (1.4–7.2)	3.7 (1.8–7.3)	2.7 (1.0–4.4)	
Median interval colonoscopy: (IQR) months	16 (11–31)	17 (12–32)	10 (7–13)	
No of intervals 12 months or less	85/237 (36%)	74/223 (33%)	11/13 (85%)	P<0.001*
Interval CRC	0	0	0	

Colonoscopy-only group vs colectomy group.  
IQR = interquartile range.

**Figure 3:** Colorectal polyps identified during serial surveillance procedures in patients managed by colonoscopy only (solid line) and patients who subsequently underwent prophylactic colectomy (dashed line).

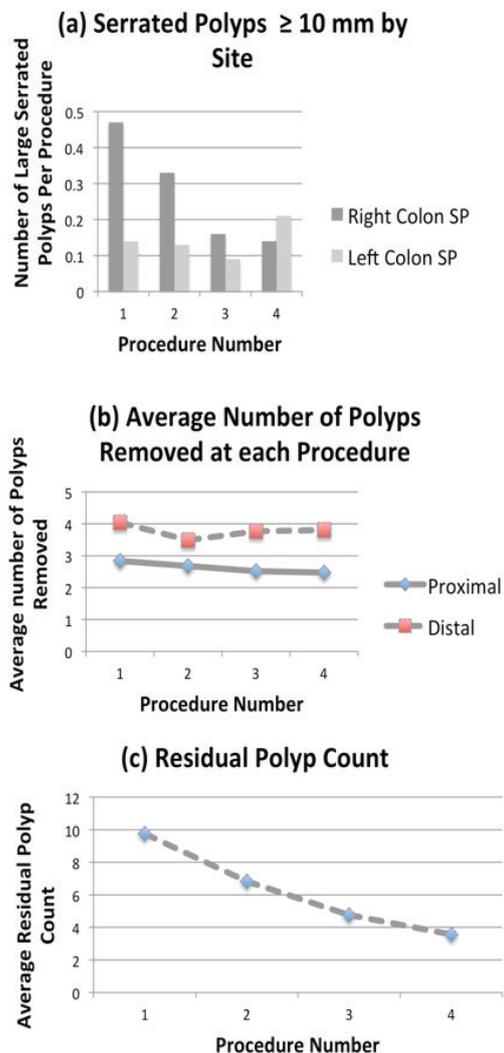


- a) average polyp count at each colonoscopy procedure
- b) polyps of any size were still detected in the proximal colon in the majority of patients at the fourth colonoscopy
- c) large serrated polyps 10mm or greater in size were still developing in 20% of patients at the fourth colonoscopy
- d) large proximal serrated polyps 10mm or greater in size were still documented in the right colon in 11% of patients at the fourth colonoscopy.

Surveillance = patients with intact colons

Colectomy = patients with intact colons who underwent a colectomy.

**Figure 4:** Colorectal polyps removed and those remaining after a procedure.



- a) proximal large serrated polyps decreased markedly over time, despite similar rates of polyp removal in both segments of the colon,
- b) the average number of polyps removed from both the proximal and distal colon at each procedure remained steady and
- c) estimated residual polyp count also decreased over time in the patients with intact colons.

were present anywhere in the colon in 20% of patients (Figure 3c), and in the right colon in 11% of patients (Figure 3d) at the fourth procedure.

Individual polyp counts at each serial procedure are depicted in Figure 4a, and

median counts for serial procedures are shown in Figure 4b, with decreasing total numbers of polyps seen over time. In contrast, Figure 4c shows no similar trend, with individual polyp counts remaining above 10.

Though serrated polyps continued to be found in the proximal colon at similar levels over time, importantly, the number of serrated lesions  $\geq 10$  mm declined sharply over four serial procedures (Figure 4a). The average number of polyps removed at each procedure in the proximal and distal colon was consistent over time, and is shown in Figure 4b. An estimate of the number of polyps remaining at the end of the procedure decreased over time from an average of 10 polyps at the first colonoscopy to an average of four polyps at the fourth colonoscopy (Figure 4c). No CRC was diagnosed in any of the patients during surveillance.

### Prophylactic colectomy patients

Five patients (four females) were referred for surgery. Multiple factors prompted referral for surgery. Failure to satisfactorily control the polyp burden, despite short intervals between colonoscopy procedures, was the overlapping reason for surgical referral in all five. In addition, three of the five patients *also* had polyps  $>20$ mm in size that were considered technically difficult to remove endoscopically, one had advanced histology (focal high-grade dysplasia) and the colonoscopy procedure itself was technically difficult for another. No CRC was identified in any of these five patients, three of whom met both WHO criteria, compared with 20/91 (22%) of patients managed by colonoscopy alone ( $p=0.07$ ). The majority of surveillance intervals in the group referred for surgery were 12 months or less (11/13 or 85%) compared with those within the group who did not go to surgery (74/223 or 33%;  $P<0.001$ ). Of interest, 5/91 patients from the group who did not go to surgery (5%) demonstrated  $>20$  polyps at fourth colonoscopy. These patients, however, also had significantly fewer short surveillance intervals (12 months or less) than those patients who were referred for surgery (6/15 or 40% vs 11/13 or 85%) ( $p=0.023$ ).

## Discussion

This study was undertaken to evaluate the efficacy of a monitored surveillance colonoscopy program to obtain control of polyps and prevent CRC in SPS patients. To date, data informing current best practice recommendations<sup>7,14</sup> have emerged out of tertiary single-centre surveillance programmes. However, it is inevitable that SPS patients, as in our study, will have colonoscopy surveillance performed by a number of different specialists with a range of expertise in varied endoscopy unit settings. In this study, colonoscopy surveillance was co-ordinated by a national tertiary service (the NZFGICS), thereby representing a more ‘real world’ setting. Our results demonstrate that, at the fourth colonoscopy procedure, surveillance with tertiary centre guidance in SPS patients with intact colons is associated with 1) a reduction in the average pan-colonic serrated polyp burden to less than 10 polyps, 2) the elimination of large polyps ( $\geq 10$ mm in size) overall in the majority (75%) of patients, especially in the right colon (almost 90% of patients), 3) the persistence/recrudescence of small polyps and 4) the necessity of referral for prophylactic colectomy in only the minority (5%) of patients. None of the patients in this study developed CRC.

For patients managed by colonoscopy alone [33% of the intervals between colonoscopy procedures were  $\leq 12$  months], the average polyp count, including small distal lesions, was  $\leq 10$  at the fourth procedure. In contrast, for patients who subsequently underwent prophylactic colectomy, despite the majority (85%) having short intervals ( $\leq 12$  months) between colonoscopy procedures, the average pan-colonic polyp count remained at  $> 20$ . This reflected the chief reason for proceeding to surgery, namely endoscopic failure to control the polyp burden. The consideration here was not only the (unknown) cancer risk, but also the higher risk of complications from frequent multiple polypectomies. For those patients in whom polyp burden was reduced successfully, and who show no high-risk features, our results suggest the colonoscopy interval could be safely increased beyond 12 months. This possibility is supported by a recent editorial, which argues for tailoring surveillance interval to risk stratification in serrated polyposis patients.<sup>11</sup>

## Persisting polyps

Our study shows that small proximal serrated polyps continue to be observed despite surveillance, and that in a small subset of patients, large proximal serrated polyps will be seen at the fourth colonoscopy. This finding has previously been described<sup>7</sup> and may reflect variability of detection of proximal serrated lesions by gastroenterologists in different endoscopy centres.<sup>9</sup> As most serrated polyps are sessile and subtle in appearance, factors besides bowel preparation, such as withdrawal time and thoroughness of examination, are likely to influence their detection.<sup>15</sup> Therefore, the perception of development of new polyps during the surveillance interval may (in part) be due to the growth of previously missed lesions.

## Risk predictors of CRC

High-risk features which predict CRC in serrated polyposis have been reported previously.<sup>16,17</sup> IJ Speert and colleagues have reported that the risk factors for CRC in the SPS setting include the presence of at least one dysplastic serrated polyp, the presence of an advanced adenoma and the concurrent presence of WHO criteria 1 and 3.<sup>17</sup> Counter-intuitively, there is evidence that not all CRC in the setting of multiple serrated polyps arise from advanced serrated lesions,<sup>13</sup> and the proportion of large serrated polyps themselves, which undergo malignant transformation if left *in situ*, is not reliably known.<sup>18,19</sup> Therefore, predicting which SPS patients are at the highest risk for CRC continues to present difficulties, particularly as surveillance modifies the natural history. This has led to the emerging and encouraging perception that the risk of CRC in SPS patients under surveillance is relatively low.<sup>20</sup> It should be noted that the five patients in our study who underwent prophylactic colectomy had revealed no evidence of malignancy. The possibility that appropriate surveillance may prevent CRC from occurring even in the presence of high-risk features may therefore exist.

## Incidence of CRC in SPS

The absence of CRC development in our study raises the question that CRC incidence in this SPS subgroup is lower than thought. This is concordant with the view that patients who develop CRC in SPS are diagnosed either synchronously with SPS

or during follow-up colonoscopy after surgery for the CRC.<sup>21</sup> This detection bias could contribute to the (high) reported CRC incidence in SPS.<sup>11</sup> Two comparable earlier, though retrospective, studies reported CRC rates of 7% in SPS patients undergoing surveillance.<sup>1,7</sup> However, they differ in not proactively removing all polyps, and the surveillance intervals were extended beyond those currently recommended. In mitigation, the time period of the Netherlands study (May 1982 to June 2008) overlapped the time before SPS was widely recognised (mid-1990s), and this would have impacted the policy on polyp removal and colonoscopy surveillance. In the other study from the US,<sup>7</sup> a longer median interval (2.0 years) was followed for patients under surveillance between the years 2001 and 2010, compared with 1.4 years in our study over a similar time period (2000–2014). However, due to intense local interest<sup>22,23</sup> SPS was well recognised and reported in New Zealand, with early dissemination of a management protocol promoting a shorter colonoscopy interval with a proactive approach to achieving polyp clearance. This may in part be responsible for the absence of CRC observed in our study, and now being confirmed by others.<sup>14,24</sup>

### Surgical intervention

The above-mentioned low rate of surgical referral for polyposis management during the 14-year study period under our protocol is an important finding. In contrast, the US study reported 27% of patients being managed with surgery.<sup>7</sup> More recently, a study from the Netherlands reported that 25% of patients were referred for surgery.<sup>17</sup> Despite our lower rate of surgical intervention (5%), and 23 patients meeting both WHO criteria 1 and 3, a known risk factor for CRC, no patient developed CRC. This question of possible surgical over-treatment has to be considered, and more work is needed to better identify those patients most at risk for CRC.

### Limitations

This study has a number of limitations related to its historical contexts and setting. Data on colonoscopy quality performance indicators were not available, although this was also the case in two previous reports

which have contributed to the current knowledge base regarding this disorder.<sup>1,7</sup> However, all colonoscopy reports were reviewed by an NZFGICS specialist and flagged if there was any concern that the procedure was incomplete, satisfactory polyp control not achieved, incomplete polyp removal noted or bowel preparation reported as poor. This resulted in recommendations for an early repeat procedure being made, and alerts created to ensure the resultant procedure report were reviewed.

Another limitation was that there was no documentation of whether or not enhanced imaging techniques were used in polyp detection at colonoscopy. This is mitigated in the light of a recent publication report that narrow band imaging does not reduce polyp miss rates in patients with SPS.<sup>25</sup>

The histological criteria for the diagnosis of serrated polyps evolved over the time of the study. No centralised retrospective histology review was performed, and polyps were only categorised by site, size and histology (serrated/hyperplastic polyps or conventional adenomas), with information on dysplasia in serrated lesions not available. Therefore, we did not separately analyse the different subtypes of serrated polyps, in particular separating hyperplastic polyps from sessile serrated adenomas. Nevertheless, the separation of serrated polyp type by size and location could be considered as surrogate markers for advanced serrated lesions. This is a reasonable strategy, bearing in mind that the current WHO definition of serrated polyposis is based on the presence of histologically confirmed serrated polyps of threshold numbers and sizes, and not on serrated polyp subtype.

Ascertainment bias is possible, as the majority of patients in this study were referred for management of polyposis and therefore met WHO criterion 3, and thus the findings of our study are likely more relevant to SPS patients with higher polyp numbers. Further limitations include median colonoscopy intervals masking the shorter intervals required initially to control the polyp burden, as well as the longer intervals where patients failed to adhere to the recommended protocol.

## Summary

In our study we observed that, under our community approach, only 5% of patients required referral for surgery, and no participant required surgical intervention for an adverse procedure-related outcome. In the majority of these patients, reduction of the average pan-colonic polyp burden to <10, the absence of polyps  $\geq 10$ mm in size in 75%, and the absence of proximal serrated polyps  $\geq 10$ mm in size in 90% of patients at the fourth procedure, was

achievable if colonoscopy was performed at intervals appropriate to the polyp burden.<sup>11</sup> Importantly, no CRC events were observed under this regimen of tertiary monitored community surveillance, a model which reflects real world practice. These findings support the general guidelines set out by the US Multi-Society Task Force on Colorectal Cancer,<sup>26</sup> which suggest yearly colonoscopic surveillance of SPS patients and the recently proposed algorithm of risk-stratified management of patients with SPS.<sup>11</sup>

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# Lip-lick dermatitis

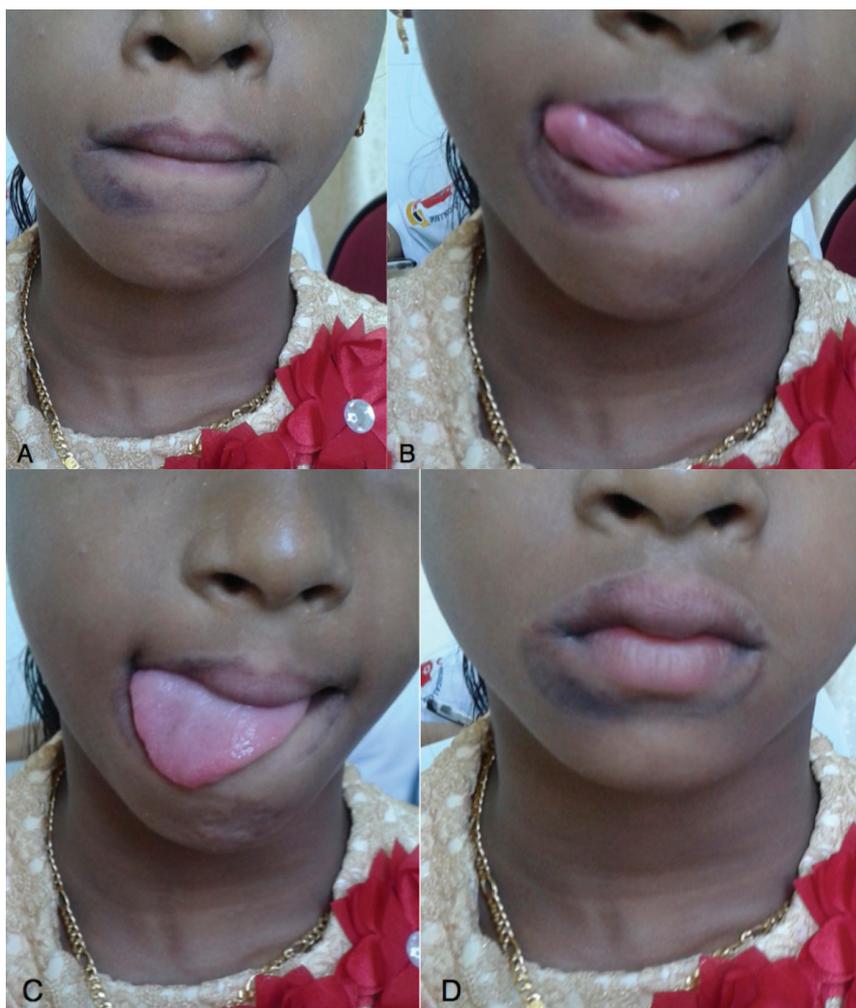
Mini PN, Anoop TM

**A**n eight-year-old girl presented with relatively asymptomatic hyperpigmented lesion over the perioral area of two months' duration. She had history of similar lesions previously during the same season. There was no history of any topical application. She acknowledged the habit of regular lip licking, as her lips feel dry. On examination, she had well defined hyperpigmented scaly plaque on the perioral area, involving the vermilion border of upper lip, but sparing a 4–5mm zone below the vermilion border of lower lip. Lips were dry and

erythematous with mild scaling of upper lip (Figure 1).

This is a case of lip-lick cheilitis seen predominantly in seven- to 15-year old age group due to habitual licking of perioral area and lips. This condition is an irritant contact dermatitis due to saliva.<sup>1</sup> Atopy, exposure to dry, cold wind causing chapping of lips and in some cases, underlying stress are predisposing factors.<sup>2</sup> Treatment primarily includes avoidance of lip licking and frequent application of emollients.<sup>3</sup>

**Figure 1:** Showing lip-lick cheilitis with hyperpigmented scaly plaque on the perioral area and lips.



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**Competing interests:**

Nil.

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# Extended follow-up of simple lymph node graft treatment of upper limb lymphoedema

Tess Brian, Winston M McEwan

## Case report

**D**uring 2009, a 65-year-old female had wide local excision of a left breast carcinoma, axillary lymph node clearance, and chemo- and radio-therapies. Long-term endocrine treatment was instigated. In 2012, recurrent carcinoma was treated by mastectomy and adjuvant chemotherapy.

The patient developed International Society of Lymphology Stage II lymphoedema of the non-dominant left upper limb. This reduced function, caused discomfort and required full-time compression sleeve wear. According to truncal cone volume calculations based on wrist and elbow circumference measurements, the affected forearm was approximately 870ml larger than the unaffected right.

During November 2013, with intravenous sedation and local anaesthetic at donor and recipient sites, the patient underwent simple Lymph Node Grafting (LNG) as treatment for this lymphoedema. Injected subcutaneous methylene blue dye was used to identify two left inguinal nodes, which were harvested for free-grafting. Through small incisions into subcutaneous tissue, one isolated node was implanted proximal to the left elbow, and the other to the distal volar forearm. The procedure took 30 minutes. Post-operative oral Flucloxacillin was prescribed. No donor limb lymphoedema or other complications occurred.

At three months post-operation, the patient declared improvement in lymphoedema symptoms. Compared with pre-operation, the left forearm volume had decreased by about 315ml. This was a 36% reduction in the extra bulk of this forearm.

The LNG procedure was repeated in September 2014. Single right inguinal nodes were transferred to each of proximal and mid volar left forearm sites. There were no complications.

In April 2016, the patient reported markedly improved sensation (tightness, heaviness, numbness) and hand and arm function, with increased ease of self-care (combing hair, dressing). She continued compression sleeve wear. The left forearm volume was approximately 580ml smaller than before the first LNG. This was a 67% decrease in the pre-surgery excess volume of this forearm over the other, which had increased by 40ml during the same period.

During June 2016, technetium tracer was injected into the skin of the left hand and distal forearm. Lymphoscintigraphy revealed tracer flowing away from both injection sites, concentrating in transplanted nodes, and exiting the limb.

## Discussion

Upper limb lymphoedema after axillary lymph node clearance and radiotherapy to treat breast cancer is common in New Zealand. The physical and psychological morbidities associated are frequent and incapacitating. Many treatments have been used to manage the condition once established, but limb compression and physiotherapy remain mainstays. Prevention or cure would bestow significant benefit to patients and the healthcare system.

Attempted cures have included microsurgical creation of drainage channels through lymphaticolymphatic and lymphaticovenous anastomoses. However, en bloc microvascular lymph node transfer in which a soft

tissue flap with its arteriovenous supply is grafted to the axilla or wrist has enjoyed most success, with very good results for some patients.<sup>1-3</sup> However, being technically difficult and time consuming, these surgeries are expensive. LNG may be an alternative.<sup>4</sup>

Skin and fat are regularly free-grafted during plastic surgery, with survival dependent on blood vessel ingrowth. The extended viability of nodes noted on lymphoscintigraphy in the LNG case reported suggests that the same occurs with this free-grafted tissue.

The substantial and incremental reduction in forearm volume of the reported patient with repeated LNG confirms efficacy of this

technique. This may occur through natural anastomosis of grafted nodes with existing limb lymphatics, with interstitial fluid accumulation in and subsequent removal from the nodes and limb via lymphaticovenous transfer.<sup>3,5</sup> It has been postulated that as well as inducing lymphatic anastomoses, these nodes may be involved in pumping lymph into the venous system.<sup>1</sup>

If, as this report suggests, LNG can achieve long-term results comparable to or better than complex microvascular surgery, at reduced risk of donor limb lymphoedema, and with the opportunity to titrate effect with repeat procedures, then it may prove useful for prevention and early treatment of cancer-related lymphoedema.

**Competing interests:**

Nil.

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# PGY2 attachments in general practice—a New Zealand experience

Dale Sheehan, J Thwaites, Vanessa Weenink, Colin Chin, Jeremy Baker

The New Zealand Curriculum Framework (NZCF) for Prevocational Training<sup>1</sup> was implemented by the Medical Council of New Zealand (MCNZ) in 2014, requiring all interns to complete one clinical attachment in a community-based setting over the course of the intern training programme, with 100% compliance by 2020. The Medical Education Training Unit (METU) at the Canterbury District Health Board (CDHB) undertook a pilot with RMOs (Post Graduate Year 2/3) doctors a year prior to the implementation to enable all parties to develop systems and processes to support community rotations in general practice.

An emergent evaluation framework developed by Haji et al<sup>2</sup> guided the design, implementation and evaluation. More importantly, it facilitated a partnership approach to placement development with the community practices and RMOs. The aim of the pilot was to determine what worked for everyone, what was reproducible and what could inform the development of future placements.

Haji's<sup>2</sup> framework guided the mixed method data collection, which included site visits, interviews with practice managers and general practitioners (GPs), pre and post face-to-face interviews with RMOs and an electronic end-of-attachment evaluation survey completed at the end of all hospital placements.

Overall the experience of RMOs and GPs in this pilot programme has been very positive and is consistent with findings from international studies.<sup>3-6</sup> A study locally undertaken in Canterbury in 2005<sup>7</sup> to determine the drivers and barriers to providing clinical attachments in general practice provided background for this initiative.

This letter shares the outcomes of this pilot with a focus on the features of the learning

environment that supported learning, the learning outcomes reported by the RMOs and the educators experience and insights. We believe these can be of assistance to others designing and managing placements.

## Features of a successful learning environment

Positive features of the learning environment identified included: RMOs having their own clinics, generous consultation times, the presence of an assigned GP who provided immediate supervision, feedback and advice. Any down time was appreciated and appeared well utilised. The practice managers had a key role in orientating the RMO to place, people and the IT system. There was an element of patient triage in assigning workload to the PGY2 doctors that ensured a good range of patients. Patient consent was not an issue having been facilitated by the practice.

## Learning gains for RMOs

RMOs stated that they gained insight into the primary-secondary care interface, the experience assisted with career choice and exposure to commonly seen, less serious clinical conditions was beneficial for learning.<sup>3-6</sup> Clinical experience identified as unique included medical screening (eg insurance, drivers medical), preparing Work and Income and Accident Compensation Corporation certificates, examining and managing children, musculo-skeletal assessment, dermatology (particularly rashes), obstetrics and gynaecology (including irregular bleeding, miscarriage) and sexual health. Pre-placement training in these areas was recommended by the RMOs.

In the three larger practices, opportunities to be part of the wider learning environment and community links, including rest homes and other agency placements, were appreciated by RMOs. In a small

practice the addition of an RMO helps build that sense of a peer community.

All felt they had a better understanding of the general practice context, the challenges faced by GPs and the interface with the hospital. They learned about the importance of the discharge summary providing clear information and instructions to the GP. The complexity of referral processes was noted. There was increased understanding of nursing and allied health roles.

### The educators experience

Evaluating the pilot within this model has ensured documentation of expectations, with co-planning through the collection of feedback on the experience and learning. Key learning points follow:

1. Expectations of both the host practices and the RMOs were identified, aligned and met as part of the evaluation process. This process of collecting information before assigning RMOs to attachments aided planning for each specific RMO and guided placement decisions. As each practice has its own culture offering a unique set of experiences and competencies, there is value in matching RMOs to placements in terms of their interests and career pathways. This is likely to be increasingly important as numbers increase toward 100% placement by 2020
2. One practice developed a response to pressure for space and rooms that worked very well for the RMOs: a half to full day community rotation where one RMO went to a physiotherapy practice, another to a child health agency. The development of sessional

visits outside the practice to gain experience with other agencies, in the community and other practices (eg physiotherapy) has merit for the future

3. A set of experiences and skills that are gained in general practice and less seen in the hospital has been identified by the RMOs (and included above). This is helpful for mapping the CDHB curriculum to the NZCF and could be incorporated into a learning module to support orientation to a GP attachment
4. Guidelines for covering periods of absence by either RMO or supervising GP are being prepared
5. The findings of the 2005 study<sup>7</sup> regarding Post Graduate Year (PGY) 2 RMOs being more suitable than PGY1 to undertake these placements was upheld and reflects the level of experience, clinical knowledge and prescribing status of PGY1 doctors.

Finally the issue of space, numbers and capacity is an ongoing one. It arose in both the 2005 study<sup>7</sup> and this project. The issue will be compounded in the future by the growing number of learners in general practices with medical students, GP registrars and increasingly nursing and allied health students seeking placement opportunities. Overall the experience for RMOs and GPs in this pilot programme has been very positive and is meeting the goals and expectations of the MCNZ. The critical question for district health boards is what financial support and resources will be required to ensure full implementation of community placements by 2020 and to ensure sustainability of the programme?

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# Learning from the ‘Muslim ban’: implications of the Trump presidency for international public health

Frank Houghton

*Mother should I build the wall?*

*Mother should I run for president?*

*Mother should I trust the government?¹*

Recently elected president of the US, Donald Trump, campaigned on a platform promising radical change within the first 100 days of his presidency. Approximately two weeks into this period it may be instructive to review changes to date and consider their implications for the future, with a particular focus on international health.

Examining domestic health issues within the US first, the new regime’s attacks on the Patient Protection and Affordable Care Act (aka ‘Obamacare’, or the ‘ACA’), which extended care to tens of millions of uninsured Americans, are well known. Promises to scrap Obamacare were a central tenet of the Republican agenda since its controversial introduction, as well as being an important element of Trump’s campaign.<sup>2</sup> The new Presidential hiring freeze on federal jobs is already having an impact on hiring, adversely impacting agencies such as the Centers for Disease Control & Prevention (CDC).<sup>3</sup> This type of restriction will in time no doubt have implications for such agencies to effectively commit to international public health operations such as the recent Ebola outbreak in West Africa.<sup>4</sup>

However, this potential distal impact is minimal compared to recent developments in the US, which seem certain to indicate a radical change in perspectives and priorities. The most important of these cultural changes is undoubtedly crystallised in the recent ‘Muslim Ban’ instigated in the US.<sup>5</sup> This executive order, which was signed on January 27<sup>th</sup>, imposed an immediate ban

for 90 days on travelers from Syria, Iran, Sudan, Libya, Somalia, Yemen and Iraq even if they held a valid residence visa, as well as suspending the entire US refugee admissions system for 120 days.<sup>6</sup>

This executive order, which is just one of many, clearly and definitively demonstrates the insecure and defensive xenophobic attitudes of Trump and the new regime. This order was hastily constructed and implemented, and quickly resulted in the firing of the US Attorney General, who questioned its legality,<sup>7</sup> as well as leaving customs officials unsure as to the status of dual nationals and those with permanent residence cards.<sup>6</sup> The new President campaigned on an extraordinary combination of uncloaked racism and insular protectionism, which has been demonstrated most strongly in his call, which became a trademark chant at his rallies, to ‘build the wall’ between the US and Mexico.<sup>8</sup>

We can therefore anticipate a continuation into the future of US policy knee-jerk reactions that are steeped in both racism and demonstrate a developing insular focus. The involvement of the US in international Public Health efforts, such as that demonstrated in response to the Ebola outbreak in West Africa, can no longer be taken for granted.<sup>9–10</sup> The current rule of Government by executive order heavily influenced by nationalist and populist politics also has significant implications for international organisations. For example, despite the important role of the United Nations (UN) in responding to the recent Ebola outbreak,<sup>11</sup> the UN has already been targeted for criticism by both Trump<sup>12</sup> and his recently appointed UN envoy.<sup>13</sup>

Trump's impact on global public health can already also be seen across a range of areas, including the removal of funding from non-governmental organisations (NGOs) that provide information on abortion.<sup>14</sup> Other impacts include a growing global insecurity,<sup>15</sup> the erosion of basic human rights,<sup>16</sup> and in examining the longer term, an increasing emphasis on fossil fuels.<sup>17</sup>

On a practical note, it must also be acknowledged that the focus of the US and many of its citizens, including those that might routinely support (financially or otherwise) international efforts in the field of health promotion, may be firmly focused internally over the next four or eight years. Many US citizens may simply have little time for international issues given their immediate focus on significant internal domestic changes. The Presidential

election result came after both a bitter and divisive campaign,<sup>18</sup> followed by a contested election result.<sup>19-20</sup>

To date the Trump presidency has been marked by controversy and clear demonstrations of populist engagement with racist sentiment. From examples in policies and commentaries so far we can expect a continuing decline in US support for international organisations such as the UN, as well as a growing isolationism. Knee-jerk policies using executive orders, with or without the support of Congress, will undoubtedly continue. US national and international health policies will increasingly be driven by right-wing capitalist and Christian principles. We can anticipate short-term and ongoing global inter-state instability, as well as longer-term implications for global warming based on a renewed emphasis on fossil fuels.

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**Competing interests:**

Nil.

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# Sunscreens

Brian Wilkins

We regularly hear calls for sunscreens to be regulated as therapeutic substances as in Australia; the most recent call being in the NZ Listener.<sup>1</sup> However, scrutiny of the standard on which this regulation is based leads to the suggestion that we could do better.

Meeting the standard, *AS/NZS 2604:2012, Sunscreen Products-Evaluation and Classification*, is voluntary in New Zealand. Some products on sale here originate in Australia and therefore comply, while some local producers comply by choice.

Evaluation uses two techniques. UV spectrophotometry measures the protection across the harmful range of wavelengths. This test has been greatly improved in recent years through the more sophisticated handling of the spectral data referring to the longer wavelengths, which can cause immunosuppression.

The other is an *in vivo* test, which depends on producing a mild burn (erythema) on the skin of human volunteers: a procedure not without long-term risk. A measured amount, 2mg/sq cm, is spread on the skin, which is then subjected to increasing timed doses of intense artificial UV irradiation. The ratio of the time to produce a just detectable redness (minimal erythema dose, MED) on the treated area compared with the MED time for the untreated area is the Sun Protection Factor (SPF).

Here we confront the weakness in the SPF method. Because of its brevity it is far from being a practical model for hours spent outdoors where sweating and muscle movement constantly threaten the integrity of the thin film. SPF is an initial value only; it tells us nothing about what happens later. Marketers have claimed that the SPF values allow users to calculate how long they could safely stay out in the sun; a dangerous lie. Pathak<sup>2</sup> showed that even after one hour of passive sunbathing the SPF would drop by about 33%, and with swimming and active exercise, by about 60%. A typical irradiation time for an SPF 30 sunscreen would be only six seconds on untreated skin and

180 seconds on coated skin. Attempts to solve these problems have involved the addition of physical activity and water immersion to the *in vivo* test, but they still fall short of modelling the actual time and conditions of use.

The question can now be asked; if the measurement of UV absorbance is precise and convenient, do we need the less convenient, less precise and more expensive SPF test? No we don't, because we already know the relationship between the two. During more than forty years we have accumulated a large amount of data relating initial SPF to UV data. Knowing the composition of the sunscreen, we can calculate the over-all UV absorbance, from which figure we can predict the approximate initial SPF; if in fact we need SPF at all. Australian workers<sup>3</sup> examining 15 products, showed a good correlation between SPF and absorbance, while the author, working independently, examined fifty products and also showed a good correlation. Attempts by others to find this relationship were plagued by the incorrect use of spectral data. Now, having found the correlation, we have no reason to keep the *in vivo* test, and can safely set up an agreed range of UV absorbance standards for manufacturers to choose from.

What about the time factor, how long the protection lasts? All protection drops off during use, more in some products than in others. Sunscreens formulated as emulsions, the most common type of formulation, carry an inherent vulnerability brought about by the necessary presence of surfactants, essentially detergents, needed for manufacturing. Unfortunately they also make it more probable that the protective film will be broken up and washed off by sweat and water. A non-emulsion formula will most likely remain on the skin longer than an emulsion-based formula, although water-repellent additives can mitigate this to some extent.

The amount of protection over time is important. Within the variable-laden field of sunscreen use in town and country, the

work-place, the beach, the sports field, the back country, the boat and the water, the time of protection is a matter best monitored out in the field through a wide variety of personal experience, not in a laboratory. Questionnaires could gather a great deal of information. Field test information

combined with UV data, relevant to user satisfaction and safety, would also include questions about skin irritation. Marketers could opt in or out of the field surveys, but the value of the results would soon be widely appreciated.

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**Competing interests:**

Nil.

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# Response to: Urinary alkalisers for cystitis—fact or fiction?

Bhally H, Bondesio K, Read K

**W**e read with interest the letter by Mr Lance Gravatt in the December 16<sup>th</sup> 2016 issue of the *Journal* titled “Urinary alkalisers for cystitis—fact or fiction?”<sup>1</sup> While the fundamental message about the lack of evidence base for routine use of alkalisers for cystitis is reflected well in the letter, there are a few points that we wish to highlight.

Firstly, there are a few inaccuracies in the introductory statement of the letter where our study<sup>2</sup> is referenced. The study setting was at Waitakere hospital in West Auckland and not Auckland City Hospital.

New cases of infection were identified over two separate 24 hour periods and not during a single day. There were 81 admissions where any infection was the primary or secondary reason for hospitalisation. Urinary tract infections (UTI) contributed to only 22% (n=18) of these cases. The letter mentions 81 UTIs instead.

The mean length of hospital stay was 5.5 and 12.5 days for medical and rehabilitation patients respectively, and not four days. Furthermore, it is our view that this reference seems to be somewhat irrelevant to the topic of this letter, which focuses predominantly on outpatient treatment of uncomplicated cystitis.

Secondly, it is worth noting that the activity of certain antibiotics may be affected by changes in urinary pH. Examples include nitrofurantoin (a commonly used antibiotic for treatment of cystitis), which has maximal antibacterial activity in acidic urine, while aminoglycosides and co-trimoxazole demonstrate greater activity against common urinary pathogens with increasing pH.<sup>3</sup>

Thirdly, we like to draw the reader’s attention to increasing use of restricted antibiotics like pivmecillinam and fosfomycin in both hospital and community settings to treat extended spectrum beta-lactamase producing (ESBL) *E.coli* and *klebsiella pneumoniae* bacteria. Such antibiotics are not affected by urinary alkalisers, and are often used when other oral options are limited due to either resistance or drug intolerance issues. A retrospective review<sup>4</sup> performed at North Shore Hospital between June 2014 and October 2015 revealed that 70 inpatients with uncomplicated ESBL UTIs (resistant also to nitrofurantoin and norfloxacin) were treated with either fosfomycin (n=42) or pivmecillinam (n=28), after the latter was chosen as the preferred antibiotic in such cases from 2015 onwards.

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**Competing interests:**

Nil.

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# Dermatitis due to Toxicodendron plants: a common occurrence during autumn

Robin Slaughter, Michael Beasley, Leo Schep

**T***oxicodendron succedaneum*, commonly called the Japanese wax or rhus tree, is a well-recognised cause of severe allergic contact dermatitis following dermal contact.<sup>1,2</sup>

These plants contain an oily resin, whose active toxins (urushiols) are potent sensitizers.<sup>3</sup> Toxicity typically occurs in the autumn when the oily resin in the plant leaves becomes enriched with the toxic principle coinciding with the leaves changing colour from green to red.<sup>4</sup> This time of year, therefore, serves as a timely reminder on the toxicity of this tree.

*Toxicodendron succedaneum* is native to Eastern Asia and belongs to the family Anacardiaceae, which is one of the most common plant families to cause allergic contact dermatitis worldwide.<sup>3</sup> Urushiols are also the incriminated agent in poison ivy (*Toxicodendron radicans*) poisonings.<sup>4</sup> *Toxicodendron succedaneum* is a small deciduous tree or large shrub which was once popular in New Zealand gardens due to its attractive scarlet autumn foliage (Figure 1). While mostly found as ornamentals in private gardens, distribution of its seeds by birds can lead to it becoming established in public areas and urban bushland.<sup>3</sup>

Urushiols are found within the entire plant including dead plant tissue.<sup>4</sup> Adverse effects can occur from skin contact, following ingestion or after inhalation of the smoke of burning plants. Additionally, dermal contact with contaminated items like clothing, animals and tools can also result in adverse effects.<sup>5</sup> Damage to the plant is necessary for the release of resin, and contact with this resin is required to induce a reaction. Slight contact with uninjured plant parts may not lead to harm,<sup>4</sup> but any

contact with *Toxicodendron succedaneum* should be avoided. Adverse reactions appear relatively common in children playing in or around the tree, and in adults while gardening or pruning.<sup>1</sup>

Following contact, symptoms usually appear within 24 to 48 hours, but onset can range from five hours to 15 days.<sup>4</sup> The principal effect is intensely pruritic erythematous papular lesions. A burning sensation, vesicles, bullae and marked oedematous reactions can follow.<sup>1,3</sup> The dermatological symptoms typically resolve within three weeks, but can last for up to six weeks in susceptible individuals.<sup>4</sup>

Initial treatment should include immediate flushing of the skin with water and a mild soap. It is recommended that thorough cleaning of the hands and under the fingernails is performed to stop further self-exposure. Absorption of urushiol is rapid; complete absorption into human skin occurs in approximately 30 minutes.<sup>4</sup> It is therefore important to promptly decontaminate the skin to minimise the level of exposure. Clothes should be completely changed,<sup>3,5</sup> and all clothing or objects that have been in contact with plant material need to be thoroughly washed with soap/detergent to prevent subsequent exposure. Symptomatic patients presenting to emergency departments can be treated with topical corticosteroids, systemic antihistamines and, if required, oral analgesics. In severe cases oral or parenteral steroids for a seven to 10 day period, followed by tapering off for another seven to 10 days, may be required.<sup>1,3,4</sup> Recurrence of symptoms can occur if the course of systemic steroids is too short.<sup>4</sup> The importance of completing the course of steroids should be emphasised to the patient.

As this illness can be debilitating, a focus on prevention is required, including identification and avoidance of these plants. Special care is required if the plant needs to be pruned or removed; protective clothing is required to cover as much of the skin as possible, and should include heavy duty vinyl gloves. Careful disposal of plant

material is also required.<sup>3,5</sup> While not officially controlled in New Zealand, it is now classed as a noxious weed in a number of Australian states. Identified specimens of noxious weeds must be destroyed to stop the spread of the plant, which is also in the interests of public health.

**Figure 1:** Branch of *Toxicodendron succedaneum* showing the characteristic bright red colour of its autumn leaves.



© Used with permission. Photo Credit: Robin Slaughter, New Zealand National Poisons Centre.

#### Competing interests:

Nil.

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# Response to: High incidence of medulloblastoma in Māori and Pacific populations in New Zealand

Peter Bradbeer on Behalf of the New Zealand Child Cancer Registry working Group of the National Child Cancer Network

**W**e read with interest the letter from Elwood and Aye.<sup>1</sup>

The New Zealand Children's Cancer Registry (NZCCR) is an ethics-approved separate resource held by the National Child Cancer Network, which contains comprehensive diagnosis, treatment, long-term effects, relapse and mortality data for all children diagnosed with cancer from 2000 onwards. There is an ongoing relationship between NZCCR and the New Zealand Cancer Registry to ensure the completeness and accuracy of child cancer incidence and survival reporting.

Elwood and Aye's findings are supported by an analysis of 2000–2007 NZCCR medulloblastoma registrations (0–14 years) presented at the Annual Congress of the International Society of Paediatric Oncology in 2011. Here, Dr Karen Tsui and colleagues reported a relative risk for Māori compared to Non-Māori of 2.7 (95% CI 1.5–5.0,  $p=0.001$ ).<sup>2</sup> In addition, there was some indication of inferior survival for Māori diagnosed with medulloblastoma, with five-year observed survival at 58% compared with 80% for non-Māori.

As Elwood and Aye note, the international literature regarding ethnic variations in medulloblastoma has previously been limited. Pleasingly, we can report that both the NZCR and NZCCR contributed to the 3<sup>rd</sup> volume of the International Incidence of Childhood Cancer, to be published in 2017, which will include sub analyses of medulloblastoma incidence according to ethnicity/race for many of the 63 countries which contributed. The rarity of childhood cancers also highlights the importance of New

Zealand's continued participation in collaborative clinical trials and biology studies that hope to further knowledge of diseases such as medulloblastoma, and possibly bring to light plausible biological bases for such differences.

Each year, clinicians who have an expertise in treating a particular tumour group are asked to review the NZCCR data fields to ensure that the information being collected is most useful in terms of patient care and research. For medulloblastoma, the NZCCR collects additional information regarding predisposing conditions, clinical staging, clinical trial participation, surgical details and chemotherapy and radiation dosages. Importantly, the biological features such as the wingless (WNT) and sonic hedgehog (SHH) pathway mutations, which Elwood and Aye note should be examined in further detail, are recorded by the NZCCR and will be included in future analyses once sufficient case numbers have accumulated.

The NZCCR Working Group is committed to supporting child cancer research and invite the authors, along with other researchers with an interest in childhood cancer, to request an NZCCR dataset. We have the unique opportunity in New Zealand to use such datasets to generate testable hypotheses regarding Māori and Pacific Island childhood cancer from susceptibility through to response to therapy.

Further details regarding the application process, along with recent NZCCR publications, can be found on the National Child Cancer Network website [www.childcancer-network.org.nz](http://www.childcancer-network.org.nz)

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**Competing interests:**

Nil.

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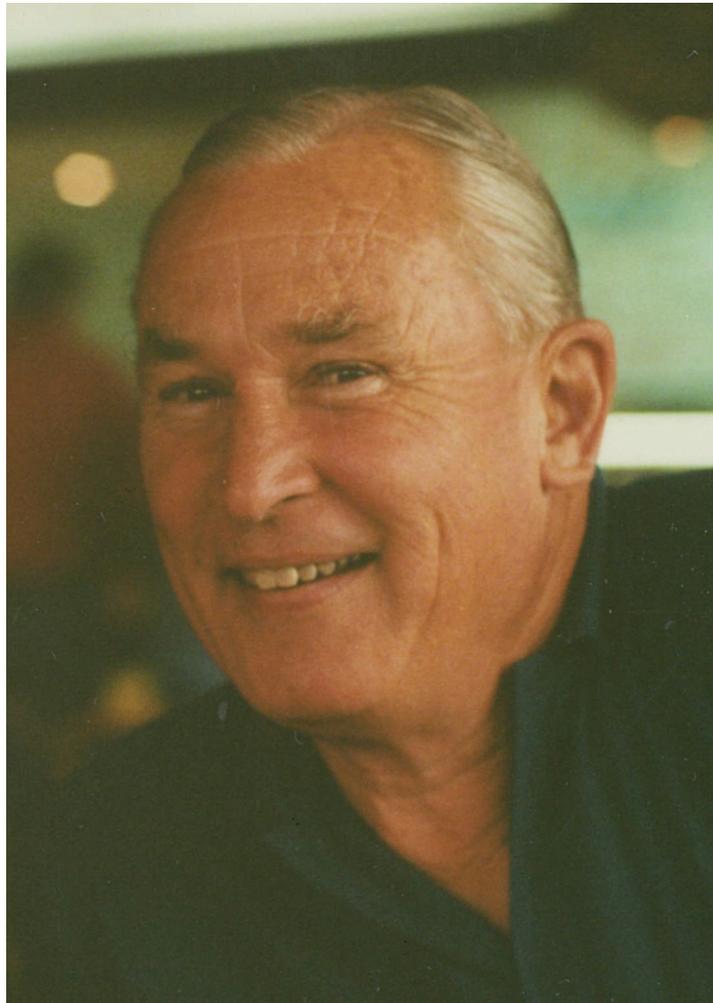
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# Milton Walters

20 November 1926–30 September 2016



**M**ilton was born 1926, Auckland. He was baptised by his grandfather, a Methodist minister, with holy water brought back from the River Jordan.

At the age of five, Milt was run over by a car and woke up in a hospital with a 'very badly broken leg and head'. He spent nearly 10 years in and out of hospital for various operations.

He lived in Mt Albert, Auckland and attended Mt Albert Grammar School where he became Head Prefect. He attended the University of Otago Medical School from 1944–1951 and then Auckland University in 1951.

He specialised in obstetrics and delivered over 5,000 babies in Northland before retiring. He was also an anaesthetist at the Whangarei Base Hospital. He set up his medical practice with Drs Walters, Brown and Bindon in Hunt Street, Whangarei.

Milt was the chairman of the NZMA's Disciplinary Committee Northland Division; he trained ambulance officers, and was made an Officer of the Order of St John and also received the Queens Service Medal.

Milt was a keen sportsman all his life, having rowed for Mt Albert Grammar and represented the school at swimming, cricket, athletics and shooting. He was

awarded six Otago University Blues and five New Zealand University Blues in rowing.

In 1948 Milt was told he was to stroke the NZ eight to the 1948 London Olympics, but the crew never met as air travel was too expensive and the voyage took five weeks by sea.

Among his many sporting interests and accomplishments, Milt was a member

of the the Northland Vikings rugby club, Vice President of the Westend Rowing Club (Auckland), and life member of the Whangarei Rowing Club, of which he was president for 32 years, and coached until 1962.

He was also a pianist and a keen card player of bridge and poker. Milt retired from medicine in 1983. He was married 64 years to Kath and loved her dearly.

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**URL:**

<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2017/vol-130-no-1451-3-march-2017/7180>

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# Misuse of drugs

## Med16/353P

### Charge

**O**n 13 and 14 September 2016, the Health Practitioners Disciplinary Tribunal heard a charge of professional misconduct laid by a Professional Conduct Committee appointed by the Medical Council of New Zealand against Dr Agnieszka Elzbieta Kleszcz, medical practitioner formerly of Auckland (the Doctor).

The charge alleged that:

- The Doctor wrote prescriptions in the name of a patient of hers for medicines which were not intended for him, and which she intended to obtain for her own use or other uses.
- The presentation of, and collection from, those prescriptions on three different dates when the medicines were not intended for the patient, that she made false claims or misrepresentations and that she intended to use the medicines for her own or other uses.
- The conduct had the potential to compromise the health and safety of the patient and/or was a breach of the Doctor's ethical and legal obligations.

While the Doctor did participate in the initial part of the Tribunal's process, she did not attend the hearing or comply with the timetable to file any documents or evidence on her behalf, prior to or at the Tribunal's hearing.

### Finding

The Doctor had during initial inquiry procedures, accepted that she had written

the prescriptions and this was also accepted by the Tribunal. The Tribunal also found that the medicines were not intended for the patient and therefore these allegations were established.

The Doctor had also denied that she was the person who attended the pharmacy on the dates in question. The Tribunal, however, found there was comprehensive and persuasive evidence to enable it to determine that the Doctor was in fact that person and upheld these allegations.

The Tribunal also found that the conduct of the Doctor did have the potential to compromise the health and safety of the patient. The conduct had the potential for the patient to have been denied medications that he was properly required to use. Others looking at the records of prescriptions in his name and supplied in his name may well have concluded that he had had sufficient of those medications and that he did not require, or was not entitled to, any when in fact he may have needed them. The Tribunal found that there were breaches by the Doctor of her ethical and legal obligations.

### Penalty

The Tribunal censured the Doctor and cancelled her registration. The Tribunal was also ordered the Doctor to pay \$21,000 towards the costs of the hearing.

The Tribunal directed publication of its decision and a summary.

The full decision of the Tribunal can be viewed on: <http://www.hpdt.org.nz/Default.aspx?tabid=503>

### URL:

<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2017/vol-130-no-1451-3-march-2017/7181>

# Pan Pacific Venous Leg Ulcer Guideline Development Group

The Pan Pacific Venous Leg Ulcer Guideline Development Group invites review and comment on the draft document *Pan Pacific Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers*, 2<sup>nd</sup> Edition.

In 2011, the Australian Wound Management Association (AWMA) (now Wounds Australia), in partnership with the New Zealand Wound Care Society (NZWCS), published the National Health and Medical Research Council-endorsed *Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers*, 1<sup>st</sup> Edition, to provide guidance on the management of venous leg ulceration in Australia and New Zealand.

The 2<sup>nd</sup> Edition is being developed under the auspice of the NHMRC through a partnership of:

- Wounds Australia
- New Zealand Wound Care Society
- Hong Kong Enterostomal Therapists Association
- Wound Healing Society Singapore.

*The Pan Pacific Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers* presented in the revised 2<sup>nd</sup> Edition provides the best available evidence, recommendations and practice points to guide practice in venous leg ulcer prevention and management.

The document contains 20 chapters, two flow charts and a glossary. Review and feedback can be provided to the full document or individual *Chapters*. Comment can be made via <http://woundguideline.com> from 3 March 2017. Please submit by 3 April 2017.

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**URL:**

<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2017/vol-130-no-1451-3-march-2017/7182>

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## Shortened antimicrobial treatment for acute otitis media in young children?

Limiting the duration of antimicrobial treatment constitutes a potential strategy to reduce the risk of antimicrobial resistance among children with acute otitis media. This report concerns a trial in which this proposition is examined.

The trialists assigned 520 children, six to 23 months of age, with acute otitis media to receive amoxicillin-clavulanate either for a standard duration of 10 days or for a reduced duration of five days followed by placebo for five days. Clinical failure of treatment was more common in the five-day cohort (34% vs 16%). Symptom scores were less in the 10-day patients. No differences were noted in the rates of recurrence, adverse events or nasopharyngeal colonisation with resistant organisms between the two groups.

The researchers conclude that among children six to 23 months of age with acute otitis media, reduced-duration antimicrobial treatment resulted in less favourable outcomes than standard-duration treatment; in addition, neither the rate of adverse events nor the rate of emergence of antimicrobial resistance was lower with the shorter regimen.

*N Engl J Med* 2016; 375:2446–56

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## Intratympanic methylprednisolone versus gentamicin in patients with unilateral Ménière's disease

Ménière's disease is characterised by severe vertigo attacks and hearing loss. Intratympanic gentamicin, the standard treatment for refractory Ménière's disease, reduces vertigo, but damages vestibular function and can worsen hearing.

Corticosteroids may also be useful in the treatment of Ménière's disease and do not harm inner ear function. Hence this trial, which aimed to assess whether intratympanic administration of the corticosteroid methylprednisolone reduces vertigo compared with gentamicin.

Sixty patients were randomly assigned to receive either gentamicin or methylprednisolone by intratympanic injection. The treatments were equally effective in reducing vertigo. Both drugs were well tolerated.

Methylprednisolone injections are a non-ablative, effective treatment for refractory Ménière's disease. The choice between methylprednisolone and gentamicin should be made based on clinical knowledge and patient circumstances. Corticosteroids would be preferred by many patients because they have no side-effects and, unlike gentamicin, are suitable in bilateral disease.

*Lancet* 2016; 388:2753–62

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## Incidence of anti-neutrophil cytoplasmic antibody-associated vasculitis before and after the February 2011 Christchurch Earthquake

It has been suggested that environmental pollution from an earthquake might be associated with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). This hypothesis is based on the prominent involvement of the respiratory tract in this vasculitis, which suggests that inhaled agents may have a role in its pathogenesis.

To test this proposition, clinicians in Christchurch reviewed the incidence of AAV in the three years before the earthquake and in the three years post-earthquake in the Canterbury region. They report no significant difference in incidence between the two study periods.

This study does not support the hypothesis that an environmental agent, caused by dust pollution related to earthquake damage, has a causative role in the pathogenesis of AAV.

*Internal Medicine Journal* 2017; 47:57–61

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<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2017/vol-130-no-1451-3-march-2017/7183>

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# Organisation for War Purposes

April 1917

At the annual meeting of members just concluded in Christchurch (the minutes of which appear in this issue of the Journal) an interesting and useful discussion took place on the question of organisation or mobilisation of the profession in New Zealand for the remainder of the war period.

Dr TA MacGibbon, the PMO for the Canterbury District, opened with a description of his recent tour through the Westland, Nelson, and Malborough Districts. He had, he said, interviewed the medical men in those districts from Hokitika to Blenheim, and it had opened his eyes to the conditions under which some medical men were working in New Zealand. His idea in making this rapid tour, lasting only a week, was to endeavour to ascertain for the Government what the possibilities were of those districts supplying more men for active service, or whether, on the other hand, the districts were in danger of being depleted of medical men. He found on the West Coast men working under conditions which those who lived in the towns could have no idea of.

On arrival at Hokitika he was immediately asked to give an anaesthetic for the local practitioner, as there was not another man available. That man had charge of a district extending 350 miles south of his location. The nearest man he could get to work with was between thirty and forty miles away. That man was prepared to go to the front if a surgeon could be provided to do his work in his absence and if he could be assured that another man would not be brought in to steal his practice. Another practitioner asked why the New Zealand Branch did not draw up some scheme of organisation such as had been brought into operation by the British Medical Association at Home. He had actually been drawn in the ballot, but did not feel disposed to appeal. It was the Association that should appeal in such cases, instead of leaving it to hospital boards, mining committees, and so on. The men in

those districts were also concerned about the introduction into Wellington recently of four medical men from the Old Country, and they asked if any action was being taken by the Association to put a stop to that kind of thing while members of the profession were making such heavy sacrifices to assist the military authorities.

Dr. MacGibbon gave details of the conditions existing in the districts referred to which went to show that those districts were becoming seriously depleted of medical men, and the members there, rightly or wrongly, felt that they were being neglected by the Association. In conclusion, he felt it was the duty of every member of the Association to assist the Government at this most critical juncture in every way possible, but a great deal more in the way of organisation was necessary on the part of the Association before satisfactory results could be achieved.

Dr. Gibbs (Hon. Secretary) said the Council had not been inactive, and, in fact, had already done a great deal in the direction of safeguarding the interests of the profession as a whole. The districts referred to had always been difficult to work, and, he understood, as far as Greymouth was concerned, there was the same number of doctors there now as had been there for the last ten years, though no doubt the surrounding district had become depleted. But the Council did recognise that the position was becoming serious, and recently, when the authorities asked for eight more medical men in addition to the regular quota, the Wellington Division on its own behalf asked for a conference with General Henderson and Dr. Valentine to go into the questions of—(1) what the requirements of the military authorities were likely to be during the next six months; (2) whether the services of the men already called up were being used economically and fully; and (3) whether an arrangement could be made for the men on active service to be relieved, after a certain period, to enable

them to resume their practices. It was felt that the military authorities were absorbing all the men and returning none for civil practice. Although that request had been made a month ago, no reply had yet been received from the Director-General of Medical Services, and the Council now felt that, as representing the Branch as a whole, it should demand a conference with the civil and military authorities, and had that day passed a resolution accordingly.

Dr. Line said if Dr. MacGibbon's tour had been made at the direction of General Henderson he did not see why the whole of New Zealand should not be toured and inspected in the same way. This might enable the General to select his men with discretion from different parts of the country.

Dr. MacGibbon said he had made the tour on his own initiative with General Henderson's consent. His object was to become acquainted with the medical men in his district. Of course, he could not divulge anything of an official nature.

Dr. Newlands said he had been acting as A.D.M.S. in the Otago District, and no instructions had been received to warrant such a tour of inspection of his district, nor, as far as he knew, had anything been done in that direction in the Southland District.

Dr. Boxer said in Hawke's Bay, on receipt of a circular from the Council, the Division had gone carefully into the position, and had, as a result, supplied General Henderson with all the information required, giving the circumstances of every man in the district. The great difficulty in the way of recruiting of medical men was the question of relief. Men were ready to sign on for twelve months. They were not professional soldiers, and should not be held by the military authorities until the end of the war. The R.A.M.C. authorities did deal with the question of relief. The men at Home were taken on for twelve or eighteen months, and then relieved with the proviso that all men not disabled shall come up for service again in rotation. The great blot on the N.Z.M.C. service was that there was no provision whatever for relief. The medical men in New Zealand wanted some assurance that their practices would not be absolutely lost to them. He felt that the Association in New Zealand should be given statutory powers to deal with all medical men whether they

were members of the Branch or not. Such a system, he understood, was working well in the Old Country. "The control of our own services," said Dr. Boxer, "should be vested in ourselves." It must be remembered that the doctors would not be demobilised for six, or perhaps twelve, months after the war. They would be kept on the chain a good deal longer than the fighting units.

Dr. Sandston did not think the Council or the Association could be held to blame for any of the difficulties that had arisen in connection with procuring medical men for the front, as the military authorities were, under present conditions, responsible for the organisation, or want of organisation, of the medical services. They were the sole arbiters. He did not know that the Committee of the B.M.A at Home had actually been given statutory powers, but the Committee worked in conjunction with the military authorities. There they required every medical man to state his exact position and what war service he had done. If he had not served he was required to state the reason why. He (Dr. Sandston) thought the New Zealand Branch should set up a committee on the lines of the Central Committee at Home, to carry out, as far as possible, the same functions and duties.

Dr. O'Brien thought it was necessary to impress upon the Government that medical men should be used for medical service only.

Dr. Gibbs said we were so far away from the seat of war, and the districts were so scattered, that he doubted whether recruiting could be effectively worked by the Association. He was afraid many of the medical men might refuse to give the required information. He would remind members that already a War Emergency Committee had been set up. Certainly it was now practically defunct, owing to the departure of most of its members for active service, and might well be remodelled.

As the outcome of the discussion, in which Drs. Irving, J. W. Crawshaw, J. H. Crawshaw, Pattie, and F. L. Scott also took part, a strong representative committee was set up to confer with the military and civil authorities.

The text of the resolution and of other important resolutions passed by the meeting will be found in the minutes published in this issue of the Journal.

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**URL:**

<http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2017/vol-130-no-1451-3-march-2017/7184>

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