Epidemiological Studies of Cervical Cancer Survival in New Zealand

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Abstract

In this thesis I describe a series of studies of the stage at diagnosis and subsequent survival of women registered with cervical cancer in New Zealand during the period 1994 to 2005, and the factors that may contribute to the demographic differences that were found in both stage at diagnosis and survival.

The studies involved all of the cervical cancer cases registered on the New Zealand Cancer Registry between 1994 and 2005. The cases were linked to the National Mortality Collection (for mortality data), the National Cervical Screening Programme-Register (for screening history), and the hospital events on the National Minimum Dataset (for information on comorbid conditions). The studies assessed what proportions of the ethnic differences in late stage diagnosis (after adjustment for socio-economic position) were due to various factors such as screening history and urban/rural residency, and what proportions of the ethnic differences in survival (after adjustment for socio-economic position) were due to various factors including stage at diagnosis, comorbid conditions, and travel time and distance to the nearest General Practitioner and cancer centre.

Māori and Pacific women had a higher risk of late stage diagnosis compared with 'Other' (predominantly European) women. Screening history did not entirely explain the increased risk in Māori women, but did explain that in Pacific women. More than half of the women with cervical cancer had not been screened, while those that had been 'regularly' screened had a considerably lower risk of a late stage diagnosis. Stage at diagnosis accounted for some but not all of the ethnic differences in survival. Comorbidity explained a moderate proportion of the ethnic differences in survival, while travel time may account for a small proportion of the ethnic differences in stage at diagnosis, and to a lesser extent mortality, particularly for Pacific women.

The higher risk of late stage diagnosis in Māori women remains largely unexplained, whereas in Pacific women it is almost entirely due to differences in screening history and travel time. More than one-half of the higher risk of mortality in Māori and Pacific women is explained by differences in stage at diagnosis and comorbid conditions.

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Abbreviations

AIS	Adenocarcinoma in situ
BDM	Births, Deaths, and Marriages
CAU	Census Area Unit
CCI	Charlson Comorbidity Index
CI	Confidence intervals
CIN	Cervical intraepithelial neoplasia
CRSR	Cumulative relative survival ratio
DAG	Directed acyclic graph
FIGO	International Federation of Gynecology and Obstetrics
GIS	Geographical Information System
GP	General Practitioner
HPV	Human papillomavirus
HR	Hazard ratio
ICD-10-AM-II	International Classification of Diseases, 10th Revision, Australian Modification, 2nd Edition
ICD-9-CM-A	International Classification of Diseases, 9th Revision, Clinical Modification (Australian version)
ICD-O	International Classification of Diseases for Oncology
km	Kilometres
LBC	Liquid-based cytology
MoH	(New Zealand) Ministry of Health
NCSP	National Cervical Screening Programme
NCSP-R	National Cervical Screening Programme-Register

NHI	National Health Index
NMDS	National Minimum Dataset
NSU	National Screening Unit
NZ	New Zealand
NZCR	New Zealand Cancer Registry
NZDep2001	New Zealand Deprivation Index 2001
OR	Odds ratio
Pap	Papanicolaou
RR	Relative risk
RSR	Relative survival rate
RSRR	Relative survival rate ratio
SEER	Surveillance, Epidemiology, and End Results
SEP	Socio-economic position
TNM	Tumour, node, metastasis
WHO	World Health Organization

CHAPTER 1

Introduction and outline of the thesis

In this thesis, I describe a series of studies of the stage at diagnosis and subsequent survival of women registered with cervical cancer in New Zealand during the period 1994 to 2005, and the factors which may contribute to the demographic differences that were found in both stage at diagnosis and survival. I start by briefly summarising the background to, and motivation for, this series of studies. I then give an outline of the thesis and the contents of each chapter.

Introduction and background

This section briefly summarises the key aspects of cervical cancer, particularly cervical cancer survival, both internationally and in New Zealand, in order to outline the background to, and motivation for, the studies presented in this thesis. In this section I will mainly focus on studies that had been published at the time that I began my series of studies (2007), but I will also include a few more recent papers that are particularly relevant.

Cervical cancer

Cervical cancer is predominantly a squamous cell malignancy, but adenocarcinomas have been increasing in incidence in some populations over the past few decades, possibly due to improvements in screening (see below) (Silverberg and Ioffe, 2003;

Vizcaino *et al*, 1998). Other malignant tumours of the cervix (including adenosquamous carcinoma, glassy cell carcinoma, adenoid cystic carcinoma, adenoid basal carcinoma, carcinoid tumour, small-cell carcinoma, and undifferentiated carcinoma) remain less common. Squamous cell carcinomas usually arise after the initial development (through multiple steps) of a precursor premalignant condition called cervical intraepithelial neoplasia (CIN), but some carcinomas appear to develop without a recognisable precursor (Hu *et al*, 2002; Silverberg and Ioffe, 2003). Adenocarcinomas usually originate from a precursor legion called cervical adenocarcinoma in situ (AIS) (Silverberg and Ioffe, 2003). Human papillomavirus (HPV) has been found to be a necessary but not sufficient cause of cervical cancer, and high risk types can be detected in 99.7% of cervical carcinomas (Walboomers *et al*, 1999). Other factors that also play a role in the development of cervical cancer include smoking, oral contraceptives, parity, sexual behaviour, and history of sexually transmitted infections (Franco *et al*, 2003; Mitchell *et al*, 1996).

Incidence and mortality

Cervical cancer is the third most common cancer amongst women in the world (after breast and colorectal cancer) with approximately 529,000 new cases in the world in 2008, representing an estimated 8.8% of incident cancers in women (Ferlay *et al*, 2010). Approximately 85% of cervical cancer cases occur in the developing world, representing around 13% of cancer in women (Ferlay *et al*, 2010). There were around 275,000 deaths from cervical cancer in 2008, about 88% of which occurred in the developing world (Ferlay *et al*, 2010). “Overall, the mortality: incidence ratio is 52%” (Ferlay *et al*, 2010).

The incidence of cervical cancer has decreased markedly in the past few decades particularly in Europe, North America and Australasia (Coleman *et al*, 1993; Vizcaino *et al*, 2000). This has occurred largely as a result of the introduction of screening programmes and early treatment of pre-invasive lesions (Devesa *et al*, 1989; Vizcaino *et al*, 2000). Cervical cancer mortality has also been falling in many developed countries, including New Zealand, since the 1950s (Beral *et al*, 1994; Coleman *et al*, 1993). Once again, these patterns are probably due to the introduction of screening programmes (Beral *et al*, 1994; Coleman *et al*, 1993; Devesa *et al*, 1989).

Cervical cancer screening

Many cases of cervical cancer appear to arise after the initial development of a precursor premalignant condition called CIN. Screening for this condition has become the main strategy for attempting to reduce mortality. The Papanicolaou (Pap) cervical smear test for cervical carcinoma was developed in the early 1940s (Papanicolaou and Traut, 1941), and first adopted in British Columbia, Canada, in 1949 (Ahluwalia and Doll, 1968). Opportunistic screening began in New Zealand in the 1950s (Donovan, 1970; Tennent *et al*, 1967) and in Great Britain, some Nordic countries, and parts of North America in the 1960s (Quinn *et al*, 1999). The first organised screening programme was introduced in British Columbia, Canada, in 1960 (IARC Working Group on the Evaluation of Cancer Preventive Strategies, 2005). Randomised controlled trials have not been undertaken to assess the effectiveness of cervical screening, but persuasive evidence comes from the Nordic countries where different screening policies were implemented and contrasting trends in incidence and mortality have since been seen (Day, 1989). Furthermore, recent randomized trials have evaluated the use of new techniques (HPV testing and liquid-based cytology (LBC)) compared with conventional

cytology (Karnon *et al*, 2004; Ronco *et al*, 2010; Siebers *et al*, 2009). Cervical screening is particularly sensitive at detecting the precursor of squamous cell carcinomas, which are the most common type of cervical cancer. Adenocarcinomas (which comprise approximately 10-15% of all cervical cancers (Vizcaino *et al*, 1998)) can be detected by cervical screening, but the endocervix is more difficult to sample and pathological identification is harder (Mitchell *et al*, 2003; Renshaw *et al*, 2004; Vizcaino *et al*, 1998).

Demographic differences

Although cervical cancer rates have been declining internationally, primarily because of the introduction of national screening programmes, there are significant disparities in cervical cancer rates by ethnicity (Akers *et al*, 2007; Garner, 2003), socio-economic position (SEP) (Akers *et al*, 2007; Eggleston *et al*, 2006; Krieger *et al*, 1999; Schwartz *et al*, 2003), and health care access (Akers *et al*, 2007; Barry and Breen, 2005). Krieger (Krieger, 2005) has developed a cancer-disparities grid to help to elucidate how certain disparity domains overlap, and may therefore contribute to inequalities across the cancer continuum. In the current context, ethnic differences in cervical cancer incidence may be related to differences in screening rates, follow-up rates of abnormal Pap smears, and treatment rates of cervical dysplasia (Akers *et al*, 2007). Ethnic treatment differentials have been reported among women from minority ethnic groups who were less likely to receive radical and definitive surgery than White women (del Carmen *et al*, 1999). Studies have reported that despite higher levels of screening amongst Black women compared with White women in North America, the incidence and mortality rates from cervical cancer remain about 2-3 times higher among Black compared with White women (Newmann and Garner, 2005). A number of studies have also reported that

ethnic minority women tend to be diagnosed at later stages of cervical cancer than White women (Newmann and Garner, 2005). These apparent contradictions may indicate a difference in the timing and manner in which ethnic groups are screened and diagnosed (Newmann and Garner, 2005). It could also be the case that because cervical cancer screening is aimed at detecting pre-cancerous lesions, and it takes about 10 years for these lesions to develop into invasive cancer, the current higher screening rates in Black women in the United States will be reflected in lower incidence and mortality rates in the future (Newmann and Garner, 2005).

Access to high quality care can have a substantial impact on cancer outcomes. Access has different dimensions and outcomes across the spectrum of cancer care, from early detection services (most often initiated in the primary care setting), to diagnostic and treatment services, to on-going surveillance and follow-up and finally, to high quality end-of-life care (Cormack *et al*, 2005; Mandelblatt *et al*, 1999). There is an extensive literature examining the relationship between SEP and access to care for cervical carcinoma (Garner, 2003). Using various markers of SEP (including income, poverty level, educational status and residency), a range of studies has found higher SEP to be associated with higher screening rates, an earlier stage at diagnosis, and decreased cervical cancer incidence and mortality rates (Eggleston *et al*, 2006; Krieger *et al*, 1999; Martin *et al*, 1996; Schwartz *et al*, 2003). While SEP appears to account for a significant proportion of the variability in cervical screening rates, disparities in these screening rates have been found to persist even after controlling for income and education, thereby suggesting a need to further understand the socio-demographic characteristics and context of the populations studied (Akers *et al*, 2007). Other studies have found insurance status to have a consistently strong effect on the receipt of both

early cancer detection and treatment services (Ayanian *et al*, 1993; Kaluzny, 1997). However, even in countries with theoretically universal access to care, women in lower SEP groups continue to have lower cancer screening and survival rates compared to those in higher SEP groups (Hart *et al*, 1998). Several explanations for the inverse relationship between SEP and cervical cancer incidence and mortality have been proposed, including the suggestion that women from lower SEP groups have limited access to high-quality medical care and screening services, as well as poor follow-up for abnormal cytology, even in situations where there is theoretically universal access to care (Akers *et al*, 2007). Additional challenges which may limit poorer women's abilities to seek or follow through with care may include lack of transport, lack of childcare, or less flexibility to take time off from their employment situation (Akers *et al*, 2007). Finally, women from a lower SEP group may have more comorbid conditions or present at a more advanced stage of disease, both of which affect treatment recommendations and tolerance (Katz *et al*, 2000).

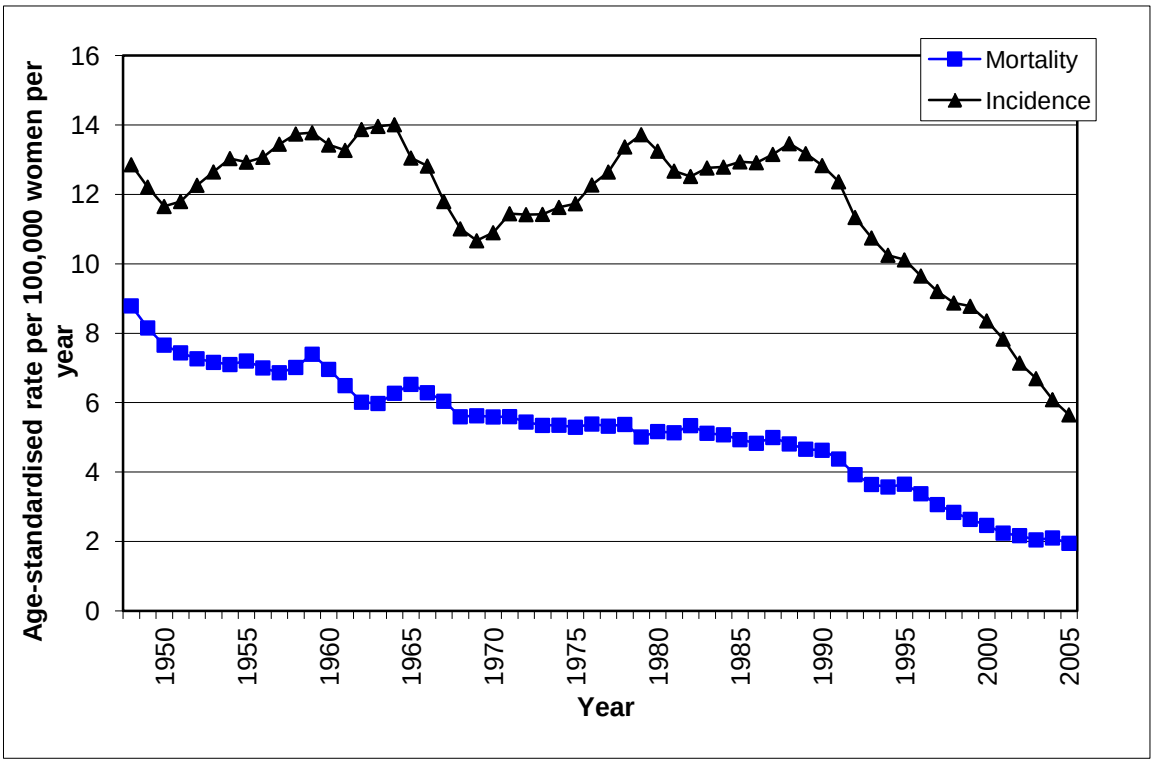
Few studies have examined the association between urban/rural residency and cervical cancer. Lack of access to health care in rural areas, due to transportation problems or fewer primary health care providers and specialist diagnostic and treatment services has been associated with reduced cervical cancer screening and treatment (Akers *et al*, 2007; Barry and Breen, 2005). Yabroff *et al* (Yabroff *et al*, 2005) suggest that rural physicians are less likely to offer cervical screening compared with their non-rural counterparts. Rural residency has also been shown to be associated with higher mortality rates (Akers *et al*, 2007; Yabroff *et al*, 2005).

Cervical cancer in New Zealand

Prior to the commencement of the studies presented in this thesis, there had been considerable debate and policy discussion on cervical cancer causes, screening and treatment in New Zealand (National Cervical Screening Programme, 2005; Paul *et al*, 2005), including various inquiries (Duffy *et al*, 2001; Paul, 1988; Paul, 2000), and audits of cases of primary invasive cervical cancer and of women with abnormal cervical smears (Priest *et al*, 2007; Sadler *et al*, 2004; Sarfati *et al*, 2003). These debates and especially the key facts and issues summarised in this section provide the background to, and motivation for, the studies presented in this thesis.

Figure 1.1 shows the five-year moving average of age-standardised (to Segi's world population) cervical cancer incidence and mortality rates per 100,000 women per year from 1948 to 2005 (figure prepared by author using data provided by the New Zealand Ministry of Health (MoH)). The Cancer Registry Act 1993 came into effect in July 1994. Incidence rates fluctuated from 1948 through to the early 1990's, when they started to decrease rapidly following the introduction of the National Cervical Screening Programme (NCSP). Mortality rates have been falling gradually from 1948, with an acceleration in the rate of decrease from the early 1990's, again subsequent to the introduction of the NCSP.

Figure 1.1. Incidence and mortality rates of cervical cancer over time



Cox (Cox, 1989) presented age specific incidence rates for cervical cancer by stage at diagnosis for the period 1976-1980. He found that the incidence rate of late stage (stages III and IV) disease rose with increasing age, and, conversely, that early stage (stage I) disease was more common in younger women. Stage I disease is more commonly diagnosed in situations where cervical screening is available because asymptomatic women who are screened will have their disease diagnosed through the screening (since this is one of the purposes of the screening), whereas if there was no screening available these asymptomatic cancers would be more likely to not be diagnosed until they became symptomatic, at which time they are more likely to be at a higher stage. The age pattern of stage distribution is therefore consistent with the fact that younger women are more intensively screened (Ratima, 1993).

Using data from the National Health Statistics Centre (now part of the MoH) Cox and Skegg (Cox and Skegg, 1986) examined trends in age specific invasive cervical cancer incidence and mortality rates for successive five-year time periods between the beginning of the 1950s and the beginning of the 1980s. They found that women aged 50 years and older had a decline in incidence rate during this period, women aged 40-49 years had a non-linear trend with high rates between 1957 and 1966, followed by a decline and then an increase (though not back to the level of 1962-1966). Women aged less than 40 years had a marked rise in incidence in the last decade examined (Cox and Skegg, 1986). These patterns are consistent with other evidence that, in cervical cancer epidemiology, there are both u-shaped birth-cohort effects and period effects due to screening (Bray *et al*, 2005a; Bray *et al*, 2005b).

Ethnic differences in incidence and mortality

Cervical cancer incidence and mortality rates have generally been declining in New Zealand over the last few decades, particularly since the introduction of the NCSP, but there continue to be ethnic differences in incidence and mortality rates.

Figure 1.2. Variations in cervical cancer incidence over time, by ethnicity

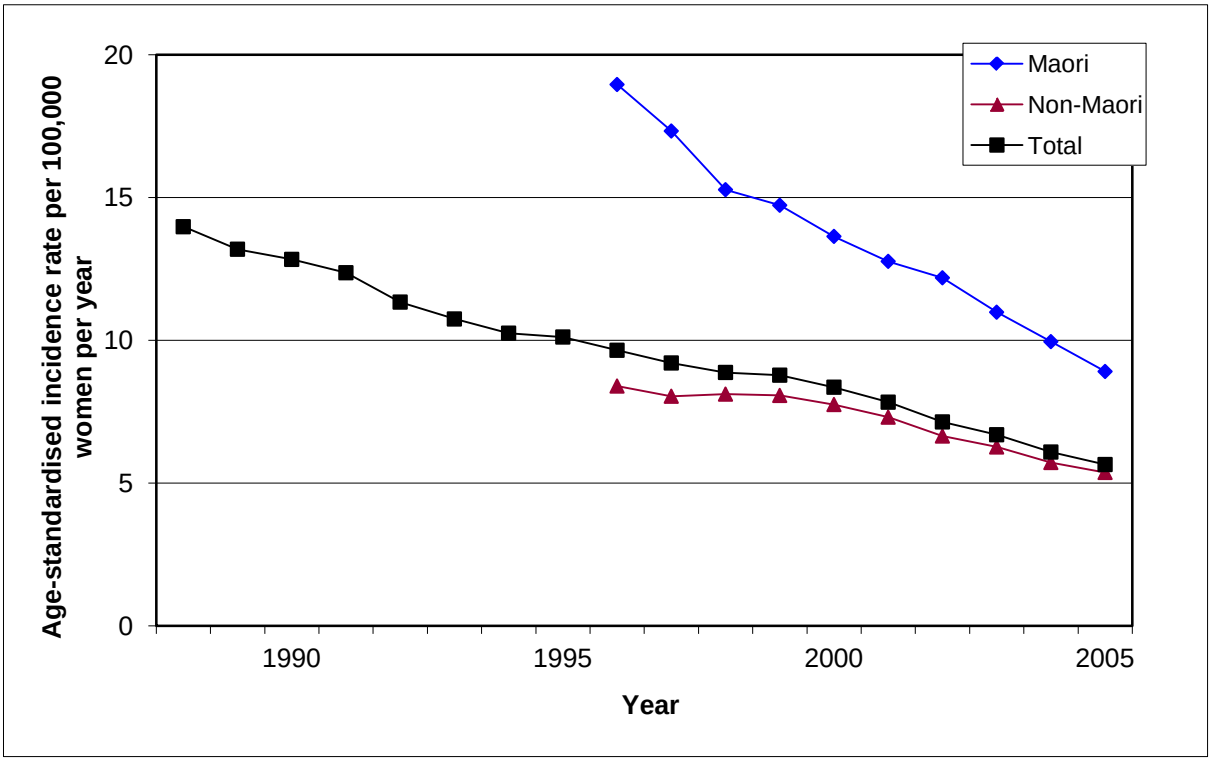


Figure 1.2 shows the five-year moving average of age-standardised (to Segi's world population) cervical cancer incidence rates per 100,000 women per year from 1988 to 2005 for all women, and from 1996 to 2005 for Māori and non-Māori women (figure prepared by author using data provided by the MoH. Please note that due to a change in the way in which ethnicity was recorded, 1995 figures are not available, and 1996 figures are not comparable to data from earlier years (which is why they are not shown) (New Zealand Health Information Service, 2006). Separate Pacific and Asian data were not available, and they are therefore included in the 'non-Māori' group. As in Figure 1.1, the incidence rate has been declining for both Māori and non-Māori women, but the Māori rates remain higher. In 1996 the age-standardised incidence rate for Māori women was 19.0 per 100,000 compared with 8.8 per 100,000 non-Māori women, hence Māori women had approximately twice the incidence rate of non-Māori women. By 2005 the age-standardised incidence rate in Māori women was 8.1 per 100,000 and that

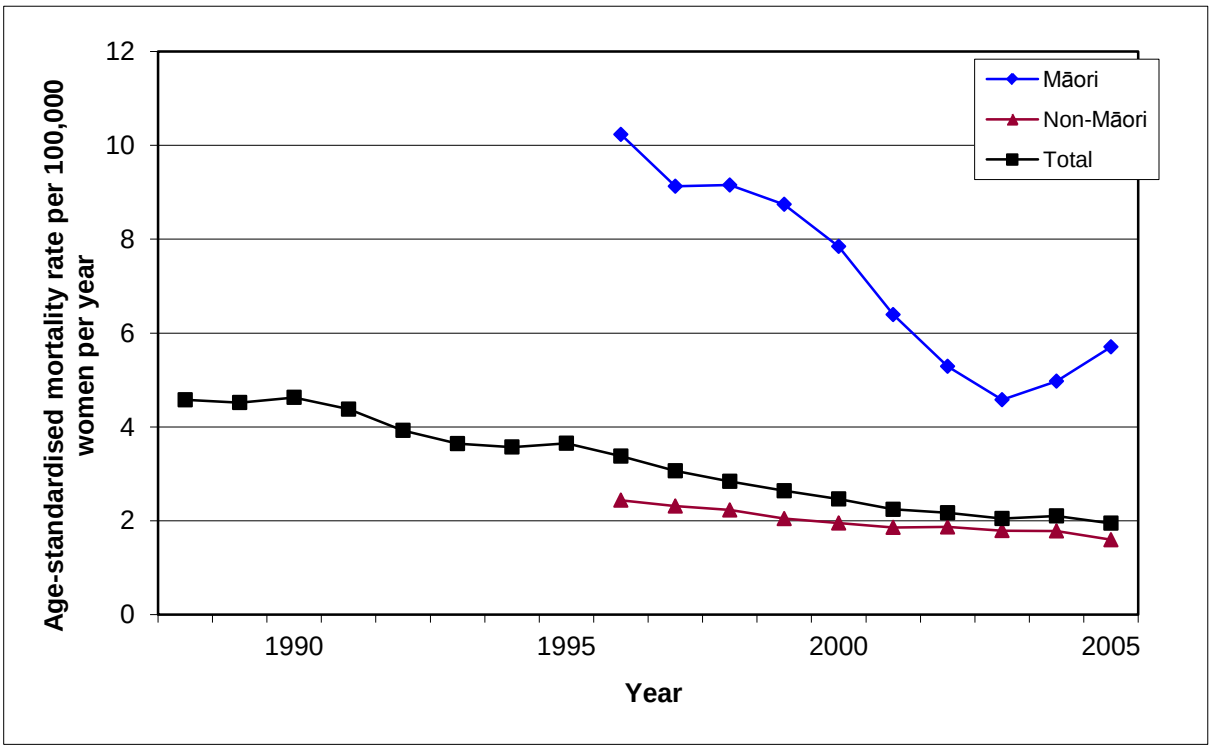
in non-Māori women was 5.3 per 100,000, hence Māori women had approximately one and a half times the incidence rate of non-Māori women. This decrease to one and a half times the incidence rate occurred only in 2005 (*i.e.* one year of data) so should be interpreted with caution. In 2007 (the latest data available), the age-standardised incidence (to the World Health Organization (WHO) standard world population) rate was 6.3 per 100,000 women (Ministry of Health, 2010a). However, the rate varied by ethnicity: 12.5 per 100,000 in Māori women compared with 5.6 in non-Māori women (Ministry of Health, 2010a). Thus, cervical cancer incidence rates are decreasing in all ethnic groups but the rate continues to be around twice as high in Māori women as it is in non-Māori women.

From 1941 to 1968, non-Māori women experienced a gradual decrease in cervical cancer mortality rates (Donovan, 1970). During this period, the mortality rate from cervical cancer in Māori women was approximately three times that in non-Māori women (Donovan, 1970).

Figure 1.3 shows the five-year moving average of age standardised (to Segi's world population) cervical cancer mortality rates per 100,000 women per year from 1988 to 2005 for all women, and from 1996 to 2005 for Māori and non-Māori women (figure prepared by author using data provided by the MoH). Once again, please note that due to a change in the way in which ethnicity was recorded, 1995 figures are not available, and 1996 figures are not comparable to data from earlier years (which is why they are not shown) (New Zealand Health Information Service, 2006). Separate Pacific and Asian data were not available, and they are therefore included in the 'non-Māori' group. As in Figure 1.1, the mortality rate has been declining for both Māori and non-Māori women, but the Māori rates remain higher. In 1996 the age-standardised mortality rate

for Māori women was 11.3 per 100,000 compared with 2.6 per 100,000 non-Māori women; hence Māori women had approximately four times the mortality rate of non-Māori women. By 2005 the age-standardised mortality rate in Māori women was 5.8 per 100,000 and that in non-Māori women was 1.4 per 100,000; hence Māori women continued to have approximately four times the mortality rate of non-Māori women. In 2007 (the latest data available) the age-standardised mortality (to the WHO standard world population) rate was 2.2 per 100,000 women and also varied by ethnicity: 4.5 per 100,000 in Māori women compared with 2.0 in non-Māori women (Ministry of Health, 2010a). Thus, the difference in the mortality rate between Māori and non-Māori women has fluctuated over recent years but appears to have decreased to a level of about two-fold.

Figure 1.3. Variations in cervical cancer mortality over time, by ethnicity



Cervical cancer screening in New Zealand

Since the declines in cervical cancer incidence and mortality rates, both internationally and in New Zealand, have, in part, been attributed to the introduction of cervical cancer screening programmes, it is natural to consider whether differences in screening provision and uptake may have contributed to the ethnic differences. I will therefore briefly discuss screening coverage in New Zealand in the following section.

Women were opportunistically screened in New Zealand from the mid-1950s (as mentioned above) (Donovan, 1970; Tennent *et al*, 1967). In 1985, a working party was convened by the Cancer Society and the Department of Health to make recommendations around cervical screening (Skegg *et al*, 1985). These recommendations were that all women who had ever had sexual intercourse should have a smear test every three years from sexual debut through to age 65 years (Skegg *et al*, 1985). In 1988 Judge (now Dame) Silvia Cartwright released *The Report of the Committee of Inquiry into Allegations Concerning the Treatment of Cervical Cancer at National Women's Hospital and into Other Related Matters* (Cartwright, 1988) which recommended that a national population-based cervical screening programme be established urgently. The NCSP was subsequently launched in 1990 and adopted the recommendations made by Skegg *et al* in 1985 (Sadler *et al*, 2004; Skegg *et al*, 1985). In 1992, new guidelines increased the maximum recommended age for participation in the screening programme to 69 years (Department of Health, 1992).

In 1992, approximately 18% of eligible Māori and non-Māori women (those aged 20-69 years who had not had a hysterectomy, except for a malignancy) were enrolled in the NCSP (meaning that they had had at least one cervical smear since the NCSP began in

1990). Enrolment increased rapidly, such that by the end of 1995 approximately 50% of eligible Māori women were enrolled in the NCSP, compared with approximately 60% of non-Māori women (Ministry of Health, 1999a). At the end of 1995, across all ages, the proportion of Māori women enrolled on the NCSP was lower than that of non-Māori women. The difference was lowest in the 20-24 year age group (Ministry of Health, 1999a). For both Māori (64%) and non-Māori (76%) women, the age group with the highest enrolment rate was the 25-29 year age group. For all women the enrolment rate (as at 31 December 1995) declined steadily with age, reaching 29% for Māori and 35% for non-Māori women aged 65-69 years (Ministry of Health, 1999a). By 1999, 89% of all eligible women were enrolled (meaning that they had had at least one cervical smear) on the NCSP (Ministry of Health, 1999b) and, in 2002, enrolment had increased to 94.9% of women (Coppell, 2006a). Five years later (in 2007, when I began my series of studies) 96% of all eligible women were enrolled on the NCSP, 79% of Māori women, 86% of Pacific women, and 100% of non-Māori/non-Pacific women (Brewer *et al*, 2008c). In each age-group, the percentage of eligible women enrolled was similar within each ethnic group, but Māori (55%) and Pacific (48%) women had the lowest proportion of enrolled women in the 20 to 24 year age group, and Pacific women had the highest proportion of enrolled women in the 35 to 39 year age group (106%; the different sources of data and population estimates used in the Independent Monitoring Report lead to estimated enrolment rates of over 100% in some age groups) (Brewer *et al*, 2008c).

At 31 December 1995, 56% of Māori compared with 62% of non-Māori women reported that they had had a smear in the three years prior to the time of their enrolment in the NCSP (this situation could arise at the beginning of the NCSP while it was being

'rolled out' but would not occur now) (Ministry of Health, 1999a). Almost the same proportion of Māori and non-Māori women reported having had a smear more than three years (20% and 19%, respectively), and 4-5 years (12% and 12.5%, respectively) before enrolment. A slightly higher proportion of Māori (7.9%) than non-Māori (6.6%) women had had a smear six or more years before, and 15.5% of Māori compared with 8.5% of non-Māori women reported never having had a smear prior to enrolment. A slightly lower proportion of Māori (8.5%) compared with non-Māori (9.9%) women had an unknown smear history at the time of enrolment (Ministry of Health, 1999a). Perhaps unsurprisingly, the highest proportion of women reporting that they had not had a smear prior to enrolling on the NCSP was in those aged 20-24 years (77% of Māori compared with 74% of non-Māori women). In women aged 30 years or more, the proportion of Māori women enrolling who had never had a smear before was higher than that in non-Māori women. At age 50-54 years, 10% of Māori women compared with 2.2% of non-Māori women had not had a smear before enrolment. In the 65-69 year age group this figure increased to 18.5% of Māori women and 4.7% of non-Māori women (Ministry of Health, 1999a).

'Coverage' of the NCSP is estimated as the number of enrolled women who have had a smear in the previous three years, as a proportion of all women. This differs from 'enrolment' which is the proportion of all women who have had at least one smear at any time since the NCSP began. Coverage increased markedly from less than 10% in 1991, when the NCSP became fully operational, to approximately 75% in 1996 (National Cervical Screening Programme, 2005). Coverage remained at about this level until 2002 (National Cervical Screening Programme, 2005) and, in 2007, it was estimated that 72% of eligible women (women aged 20-69 years who have not had a

hysterectomy, except for a malignancy) had had a cervical smear in the last three years (*i.e.* were 'covered' since the NCSP recommends screening every three years) (Brewer *et al*, 2008c). In 2003, coverage varied by age, with women aged 20-24 years having the lowest coverage (60%), increasing to a peak of 85% among women aged 55-59 years, and then decreasing again to 65% in women aged 65-69 years (National Cervical Screening Programme, 2005). This age pattern was also evident in 2007 (Brewer *et al*, 2008c). Coverage also varies by ethnicity. In 2001 'Other' (predominantly European) women had a hysterectomy-adjusted coverage proportion of approximately 78%, Māori women 51%, and Pacific women 49% (data were not available for Asian women) (National Cervical Screening Programme, 2005). Again, the pattern was similar in 2007 with non-Māori/non-Pacific women having an estimated hysterectomy-adjusted coverage proportion of 77%, Māori women 48% and Pacific women 48% (Brewer *et al*, 2008c). There is also evidence that coverage varies by SEP. The 2002/2003 New Zealand Health Survey (which involved face-to-face interviews with 12,929 adults between September 2002 and January 2004) found that the least-deprived women had a coverage rate of approximately 79% whilst the most deprived women had a coverage rate of approximately 66% (Ministry of Health, 2004b). This pattern continued in the 2006/2007 New Zealand Health Survey where the most-deprived women were significantly less likely than the least-deprived women to have had a cervical smear in the last three years (Ministry of Health, 2008b).

Cervical cancer survival in New Zealand

Cervical cancer survival in New Zealand has been improving over time; five-year relative survival rates increased from about 69% for cases diagnosed in 1997-1998 to about 75% for cases diagnosed in 2005-2006 (Ministry of Health and Minister of

Health, 2007). There is historical evidence of differences in cervical cancer mortality between Māori and non-Māori women, with some evidence that these may be due, in part, to differences in cervical cancer survival (Jeffreys *et al*, 2005b; Robson and Harris, 2007; Robson *et al*, 2006). It is particularly noteworthy that the relative risk for cervical cancer mortality in Māori women (compared with non-Māori women) is greater than the corresponding relative risk for cervical cancer incidence, and Māori women are more likely than non-Māori women to be diagnosed with cervical cancer at a late stage (Robson and Harris, 2007; Sadler *et al*, 2004).

Using data from 1994 to 2003, the MoH (Ministry of Health, 2006) estimated five-year cervical cancer cumulative relative survival ratios (CRSRs) of 0.63 for Māori women, 0.83 for non-Māori women, and 0.72 for all women. The five-year CRSRs differed by the extent of disease at registration, with localised disease having a CRSR of approximately 1.0, regional disease having a CRSR of approximately 0.7, and distant disease having a CRSR of approximately 0.1 (Ministry of Health, 2006). Interval-specific relative survival ratios were also estimated: for Māori women they were 0.81 at one year since diagnosis; 0.88 at two years; 0.96 at three years; 0.95 at four years; and, 0.96 at five years. The corresponding estimates for non-Māori women were: 0.89; 0.92; 0.95; 0.97; and, 0.97 (Ministry of Health, 2006). The report did not present relative survival estimates for Pacific or Asian women or by SEP, and nor were they presented by ethnicity and extent of disease, or any other combinations of these factors.

Jeffreys *et al* (Jeffreys *et al*, 2005b) studied ethnic inequalities in cancer survival in New Zealand. They estimated age-standardised relative survival rates (RSRs) with 95% confidence intervals (95% CI) for the 20 main cancer sites combined and for each site

separately. Relative survival rate ratios (RSRRs), comparing Māori to non-Māori/non-Pacific people were standardised first for age and then for age and stage at diagnosis. The age-standardised 5-year RSRs (95% CI) for cervical cancer cases with stage recorded were 0.73 (0.66-0.79) in Māori and 0.87 (0.84-0.89) in non-Māori/non-Pacific people (Pacific people were excluded due to small numbers). Stage at diagnosis made little difference to the RSRR estimates (age-standardised RSRR 0.84, age- and stage-standardised RSRR 0.87) (Jeffreys *et al*, 2005b).

There was also some evidence of (smaller) socio-economic differences in incidence (McFadden *et al*, 2004) and survival (Jeffreys *et al*, 2009; Jeffreys *et al*, 2005a). To investigate the role of the extent of disease at diagnosis on the socio-economic differences in cervical cancer survival (along with 19 other cancer sites) Jeffreys *et al* (Jeffreys *et al*, 2009) computed age-standardised and age- and extent-standardised 5-year RSRs by quartiles of deprivation for people that had extent of disease data recorded on the New Zealand Cancer Registry (NZCR; 35% of cervical cancer registrations did not have extent of disease recorded). The age-standardised 5-year RSRs (95% CI) for cervical cancer were 0.83 (0.78-0.88) in deprivation quartile 1 (least deprived), 0.80 (0.72-0.89) in quartile 2, 0.74 (0.69-0.79) in quartile 3, and 0.80 (0.73-0.87) in quartile 4. The deprivation gap (an estimation of the difference between the hypothetically most-deprived and least-deprived persons) was -0.10 (-0.41–0.21, p=0.29) (Jeffreys *et al*, 2009). Standardising for extent of disease made a small difference to these findings: age- and extent-standardised 5-year RSRs (95% CI) 0.80 (0.76-0.83) for quartile 1, 0.76 (0.72-0.80) quartile 2, 0.75 (0.71-0.79) quartile 3, and 0.82 (0.78-0.85) quartile 4. The deprivation gap was 0.00 (-0.30–0.31, p=0.97) (Jeffreys *et al*, 2009). It is possible that

the amount of missing data on extent of disease may have led to an underestimation of the deprivation gap.

New Zealand datasets on cervical cancer screening, incidence and mortality

Thus, prior to the commencement of this thesis, there was evidence of differences in cervical cancer incidence and mortality between Māori and non-Māori women, which may be due in part to differences in cervical cancer survival (Jeffreys *et al*, 2005b; Robson and Harris, 2007; Robson *et al*, 2006). These differences are explored in more depth in this thesis, together with other possible demographic differences, such as SEP and urban/rural differences, which had not previously been assessed. In this section, I describe the data sets that were used for this work. These were the NZCR, the National Mortality Collection, the National Cervical Screening Programme-Register (NCSP-R), and the hospital events on the National Minimum Dataset (NMDS).

The NZCR is a population-based register of all primary malignant tumours diagnosed in New Zealand, excluding squamous and basal cell skin cancers (Ministry of Health, 2010b). It was established in 1948, and the Cancer Registry Act came into effect in 1994, making cancer registration mandatory (Ministry of Health, 2002; Ministry of Health, 2009a). The NZCR is a member of the International Association of Cancer Registries and has satisfied the criteria for data quality for their data to be published in the *Cancer Incidence in Five Continents* series (Giles and Thursfield, 2004; Giles, 2004; The Descriptive Epidemiology Group of IARC, 2008). Pathology laboratories are the primary source of cancer data to the NZCR, and other collections (medical certificates of causes of death, coroners' findings, public hospital discharge data, and

private hospital discharge returns), as well as extensive data checking, are used to validate the cancer diagnoses (New Zealand Health Information Service, 2004). The NZCR uses international cancer registration guidelines for assigning date of diagnosis, and a recent study has shown 97.3% agreement within 6 weeks between the NZCR diagnosis date and clinical notes data (Cunningham *et al*, 2008). Several studies recently demonstrated a high level of agreement in most areas of data collection between the NZCR and the other sources of information (*e.g.*, regional databases and clinical records) used to assess the validity of the registrations and the accuracy of ethnicity data held by the NZCR (Cunningham *et al*, 2008; Douglas and Dockerty, 2007; Stevens *et al*, 2008a).

The NZCR records self-identified ethnicity, where people may record multiple responses, based on the Statistics New Zealand Census ethnicity question (the data utilized in this thesis used the ethnicity definitions of the 1991, 1996, and 2001 Censuses, and there were minor differences in the wording of the questions between Censuses) (Ministry of Health, 2004a). Patients who report more than one ethnicity are classified into a single ethnicity using a standard system of prioritization: Māori>Pacific>Asian>Other (New Zealand Department of Statistics, 1990). Participants with missing ethnicity data are included in the Other (predominantly European) ethnic group in the analyses presented in this thesis, as is standard practice in New Zealand health research (Ministry of Health, 2002; Ministry of Health, 2006).

The potential problems of misclassification of ethnicity data are also discussed in the chapters that follow (particularly Chapter 2), and will only be considered briefly here. Misclassification of ethnicity is a potential problem with data from the NZCR, and has

been estimated as a 17% undercount of Māori cancer registrations (Cormack *et al*, 2005) (this involves misclassification of ethnicity on registrations rather than case under-ascertainment). Thus, the 'Other' ethnic group may contain some Māori cases that were incorrectly classified, thereby diluting any ethnic survival differences. As noted above, the classification of ethnicity was based on the wording of the corresponding Census questions, and these have changed over time; once again, however, this is unlikely to have produced serious bias in the work presented here, because the ethnicity recorded on the NZCR was also used to classify the corresponding deaths, and the analyses were adjusted for registration year.

The National Mortality Collection holds information on all deaths registered in New Zealand from 1988 onwards. It was "established to provide data for public health research, policy formulation, development and monitoring, and cancer survival studies. A complete dataset of each year's mortality data is sent to the World Health Organization each year to be used in international comparisons of mortality statistics" (Ministry of Health, 2009b). The Collection classifies the underlying cause of death for all deaths registered in New Zealand using the International Classification of Diseases, 10th Revision, Australian Modification 2nd Edition (ICD-10-AM-II) and the WHO Rules and Guidelines for Mortality Coding (Ministry of Health, 2009d). Causes of deaths for death registrations before 2000 are recorded in International Classification of Diseases, 9th Revision (Australian version) (ICD-9-CM-A) and have not been mapped forward to ICD-10-AM. The underlying cause of death, as defined by WHO is "... the disease or injury which initiated the train of morbid events leading directly to death or the circumstances of the accident or violence which produced the fatal injury" (New Zealand Health Information Service, 2006). "Each month Births, Deaths, and Marriages

(BDM) sends [the MoH] electronic death registration and electronic stillbirth information data (for the previous month's registrations), Medical Certificates of Causes of Death ... and Coroners' reports" (Ministry of Health, 2009d). Further information on underlying cause of death is obtained on an on-going basis from electronic hospital discharge data from the NMDS and private hospital discharge returns, post-mortem reports from private pathologists and hospitals (New Zealand Health Information Service, 2006), the NZCR, the Department for Courts, the New Zealand Police, the New Zealand Transport Agency, Water Safety New Zealand, Media Search, death registration forms which are usually completed by the funeral director (New Zealand Health Information Service, 2006), "and from writing letters to certifying doctors, coroners, and medical records officers in public hospitals" (Ministry of Health, 2009d).

The NCSP-R is a database managed by the National Screening Unit (NSU) of the MoH (the NSU run the NCSP). The purpose of the register to is enable access to information by those running or evaluating the NCSP and, as with the NCSP, to reduce the incidence and mortality rate of cervical cancer in New Zealand (National Screening Unit, 2009). The NCSP-R holds demographic, contact, cervical and treatment details so that women participating in the NCSP can be correctly identified, and so that the NSU can determine when the women need to have their next smear or if follow-up is required, and also so that the NSU can write to the women to remind them if they are overdue for a smear or need follow-up (thus, it acts as a backup service to General Practitioners (GPs)). It also generates screening histories for smear takers, laboratories and colposcopists, and provides confirmation to women who have enrolled (or have cancelled their enrolment) in the Programme, as well as providing statistical data for monitoring and evaluation of the Programme (National Screening Unit, 2009). The

NCSP-R is governed by the Health (National Cervical Screening Programme) Amendment Act, which came into effect in 2004, and stipulates that all cervical cytological and histological test results must be sent to the NCSP (for entry onto the NCSP-R), unless the woman chooses to withdraw her enrolment from the programme (please see the '*Methodological issues and limitations*' section, page 137, for further information).

The NMDS contains national public and private hospital discharge information, including coded clinical information, for inpatients and day patients (Ministry of Health, 2009c). The data from the NMDS is used to create policy, for performance monitoring, research and review. Using the NMDS the MoH can produce statistical information and reports about "trends in the delivery of hospital inpatient and day patient health services both nationally and on a provider basis. It is also used for funding purposes" (Ministry of Health, 2009c). The NMDS in its current form was established in 1999, but the collection was introduced in 1993, and contains public-hospital discharge information from 1988. It holds information on publicly funded events from private hospitals from 1997 (National Health Board Business Unit, 2010). The publicly funded hospital events data are entered onto the NMDS within 21 days after the month of discharge, and processing of this data therefore occurs almost every day. Private hospital data are also frequently updated (Ministry of Health, 2009c).

Outline of the thesis

As stated above, prior to the commencement of this thesis, there was evidence of considerable differences in cervical cancer incidence and mortality between Māori and

non-Māori women, which may be due in part to differences in cervical cancer survival (Jeffreys *et al*, 2005b; Robson and Harris, 2007; Robson *et al*, 2006). Similar findings had been observed for other cancer sites (Jeffreys *et al*, 2009; Jeffreys *et al*, 2005a; Jeffreys *et al*, 2005b; Robson and Harris, 2007; Robson *et al*, 2006; Sneyd, 2008). There was also some evidence of (smaller) socio-economic differences in incidence (McFadden *et al*, 2004) and survival (Jeffreys *et al*, 2009; Jeffreys *et al*, 2005a). It was particularly noteworthy that the relative risk for cervical cancer mortality in Māori women (compared with non-Māori women) was greater than the corresponding relative risk for cervical cancer incidence, and Māori women were more likely than non-Māori women to be diagnosed with cervical cancer at a late stage (Robson and Harris, 2007; Sadler *et al*, 2004). However, the corresponding analyses had not been conducted for Pacific and Asian women in New Zealand. Furthermore, only limited studies had been undertaken about screening history, (Ratima *et al*, 1993) and no analyses had been conducted of other relevant factors such as travel time and distance, and comorbid conditions. It was therefore decided to conduct a systematic series of studies of the stage at diagnosis and subsequent survival of women registered with cervical cancer in New Zealand, and the factors which contribute to the demographic differences that were found in both stage at diagnosis and survival.

The five chapters are presented in the format of manuscripts for peer-reviewed publication, and there is, therefore, some repetition between the chapters, particularly in the introduction and methods sections. There are differences in the following chapters in the way in which the exclusions of cases are described. This occurs partly because in some instances the women were missing information about more than one variable (and the initial variable for which they were excluded is described differently), and partly

because in Chapter 3 no survival analyses were performed and cases therefore did not need to be excluded because they had a potential follow-up time of less than six-months.

The first manuscript (Chapter 2) investigates the associations between ethnicity, SEP and urban/rural residency, and cervical cancer survival. For each of these demographic factors, I assess how much of any excess mortality risk is explained by the other demographic factors (*e.g.* how much do the ethnic inequalities reduce when adjusted for SEP and urban/rural residency), and examine how much is explained by differences in stage at diagnosis.

The second manuscript (Chapter 3) investigates the associations between screening history and stage at diagnosis.

The manuscript presented in Chapter 4 describes the associations of comorbid conditions with cervical cancer survival, and assesses whether comorbidity accounts for the ethnic differences in survival.

The fourth manuscript (Chapter 5) investigates whether travel time or travel distance to the nearest GP and/or cancer centre accounts for the ethnic differences in cervical cancer screening, stage at diagnosis and mortality in New Zealand.

Chapter 6 (the fifth manuscript) then presents a comprehensive analysis of the relative importance of all of the factors under consideration, (*i.e.* screening history, comorbid conditions, and travel time to the nearest GP or cancer centre), in cervical cancer stage

at diagnosis and subsequent survival, and examines the extent to which the effects of these factors may be mediated through their effects on stage at diagnosis or may affect cancer survival more directly.

Finally, in Chapter 7, I summarize the findings of the new research that was conducted for this thesis, and discuss the public health implications, the policy implications, and the priorities for future research.

CHAPTER 2

Demographic differences in stage at diagnosis and cervical cancer survival in New Zealand, 1994-2005

Naomi Brewer, Neil Pearce, Mona Jeffreys, Paul White, Lis Ellison-Loschmann

Objective: To investigate ethnic, socio-economic and urban/rural differences in stage at diagnosis and cervical cancer survival in New Zealand.

Methods: The study involved 1,594 cervical cancer cases registered during 1994-2005. Cox regression was used to estimate adjusted cervical cancer mortality hazard ratios (HRs).

Results: Māori and Pacific women had higher death rates than 'Other' (predominantly European) women, with age and registration year adjusted HRs of 2.15 (95% confidence intervals 1.68-2.75) and 1.98 (1.25-3.13) respectively, whereas Asian women had a lower (non-statistically significant) risk (0.81, 0.47-1.42). Adjustment for stage reduced the HR in Māori to 1.62 (1.25-2.09), but there was little change for Pacific or Asian women. These patterns varied over time: for cases diagnosed during 1994-1997, the HR for Māori women was 2.34 (1.68-3.27), which reduced to 1.83 (1.29-2.60) when adjusted for stage; for cases diagnosed during 2002-2005, the corresponding estimates were 1.54 (0.75-3.13) and 0.90 (0.43-1.89). Socio-economic position and urban/rural residency had only marginal effects.

Conclusions: There were major ethnic differences in cervical cancer survival in New Zealand that were only partly explained by stage at diagnosis. These patterns varied over time, with post-diagnostic factors playing an important role in the high Māori mortality rates in the 1990s, but in more recent years, the excess mortality in Māori women appeared to be almost entirely due to stage at diagnosis, indicating that ethnic differences in access to and uptake of screening and treatment of pre-malignant lesions may have been playing a major role.

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Introduction

In 2004, cervical cancer was the thirteenth most common site of cancer registration and death for New Zealand females (New Zealand Health Information Service, 2007), and the incidence and mortality rates were moderately high compared with the rest of the developed world (The Descriptive Epidemiology Group of IARC, 2002). Over the last decade, New Zealand's rates of cervical cancer have been decreasing (Brewer *et al*, 2008b; National Cervical Screening Programme, 2005), with the data for 2005 showing an age-adjusted incidence rate of 6.2 and an age-adjusted mortality rate of 1.9 per 100,000 women of all ages (New Zealand Health Information Service, 2008). The most likely reason for these decreases is the establishment in 1991 of the New Zealand National Cervical Screening Programme (NCSP) (Paul *et al*, 2005). The NCSP recommends that all women aged 20-69 years have a cervical cytology test once every three years (National Screening Unit, 2008).

There are considerable differences in cervical cancer survival between Māori and non-Māori women (Brewer *et al*, 2007a; Jeffreys *et al*, 2005b; Robson and Harris, 2007; Robson *et al*, 2006). The reasons for these differences are not entirely clear, with some reports indicating that stage at diagnosis accounts for most of the survival difference, and others indicating that it explains only a small amount of the difference in relative survival rates between Māori and non-Māori/non-Pacific women (Brewer *et al*, 2007a; Jeffreys *et al*, 2005b; Robson and Harris, 2007; Robson *et al*, 2006). Furthermore, the corresponding analyses have not been conducted for Pacific and Asian women in New Zealand.

In the United States, socio-economic position (SEP) has been shown to be independently associated with stage at diagnosis and cervical cancer survival, and this may explain some of the ethnic differences that have been observed (Akers *et al*, 2007; Eggleston *et al*, 2006). Rural residency, which can be seen as a proxy for access to care as there may be fewer primary health care providers as well as specialist diagnostic and treatment services, has also been shown to be associated with higher mortality rates (Akers *et al*, 2007; Yabroff *et al*, 2005). However, analyses of stage at diagnosis and cause-specific cervical cancer survival by SEP or place of residency have not been conducted in New Zealand. Furthermore, although these demographic factors are of importance in themselves, it is also of interest to determine to what extent the previously reported ethnic differences may be explained by SEP or place of residency or both.

Therefore, the current study was undertaken in order to conduct a comprehensive analysis of demographic differences in stage at diagnosis and cervical cancer survival in New Zealand between 1994 and 2005.

Materials and Methods

The source population comprised all cervical cancer cases registered with the New Zealand Cancer Registry (NZCR) between 1 January 1994 and 30 June 2005. The NZCR was established in 1948, and the Cancer Registry Act 1993 came into effect in July 1994 making cancer registration mandatory (Ministry of Health, 2002; Ministry of Health, 2008a). The NZCR is a member of the International Association of Cancer Registries and has satisfied the criteria for data quality for their data to be published in

the *Cancer Incidence in Five Continents* series (Giles and Thursfield, 2004; Giles, 2004; The Descriptive Epidemiology Group of IARC, 2008). Pathology laboratories are the primary source of cancer data to the NZCR, and other collections (medical certificates of causes of death, coroners' findings, public hospital discharge data, and private hospital discharge returns) as well as extensive data checking are used to validate the cancer diagnoses (New Zealand Health Information Service, 2004). The NZCR uses international cancer registration guidelines for assigning date of diagnosis (Susan Hanna, Team Leader, NZCR, personal communication, November 2004), and a recent study has shown 97.3% agreement within six weeks between the NZCR diagnosis date and clinical notes data (Cunningham *et al*, 2008). Several studies recently demonstrated a high level of agreement in most areas of data collection between the NZCR and the other sources of information (*e.g.* regional databases and clinical records) used to assess the validity of the registrations and the accuracy of ethnicity data held by the NZCR (Cunningham *et al*, 2008; Douglas and Dockerty, 2007; Stevens *et al*, 2008a). All registrations include the National Health Index (NHI) number that uniquely identifies individual health care users; this was used to obtain cause-specific mortality data (from the Mortality Collection) up to the end of December 2005 (the most recent year for which data were available).

The New Zealand Central Ethics Committee reviewed the study protocol and granted ethical approval for the study.

The NZCR records self-identified ethnicity, where people may record multiple responses, based on the Statistics New Zealand Census ethnicity question (the data in the current analyses used the ethnicity definitions of the 1991, 1996 and 2001 Censuses,

and there were minor differences in the wording of the questions between Censuses) (Ministry of Health, 2004a). Participants who reported more than one ethnicity were classified into a single ethnicity using a standard system of prioritisation: Māori>Pacific>Asian>'Other' (New Zealand Department of Statistics, 1990). Participants with missing ethnicity data were included in the 'Other' (predominantly European) ethnic group in the analyses. This approach is standard practice in New Zealand health research (Ministry of Health, 2002; Ministry of Health, 2006).

SEP was estimated using the New Zealand Deprivation Index 2001 (NZDep2001) (Crampton *et al*, 2004). NZDep2001 is a small-area composite score based on nine variables (benefit income, employment, household income, communication, transport, support, qualifications, living space, and home ownership) taken from the 2001 New Zealand Census. Each participant was assigned a score based upon the residential area in which she lived (the domicile code) as recorded on the NZCR at the time of registration. These scores were then grouped into quintiles, with a value of 5 indicating that the area is in the most deprived 20 per cent of small areas in New Zealand as measured by NZDep2001 (Crampton *et al*, 2004).

The domicile code recorded for each participant was also used to assign urban/rural residency according to population size, based on the Statistics New Zealand classification (Statistics New Zealand, 2008). Participants were classified as living in a main urban area (with a population of ≥30,000), a secondary or minor urban area (population ≥1,000 to 29,999), or a rural area (population <1,000).

Stage at diagnosis was obtained from the NZCR. Of the 2,260 cases occurring between January 1994 and June 2005, 52% had a differentiation grade code (developed by the New Zealand Health Information Service) (New Zealand Health Information Service, 2004), 64% had a Surveillance, Epidemiology, and End Results (SEER) code (Young *et al*, 2001), and 74% had an International Federation of Gynecology and Obstetrics (FIGO) code (Benedet *et al*, 2006). Less than 1% of records contained tumour, node, metastasis (TNM) codes (the staging system developed and maintained by the American Joint Committee on Cancer). Preliminary analyses were conducted with the subgroup of 1,086 patients who had both a SEER code and a FIGO code recorded, as well as the other variables being considered. These analyses yielded similar hazard ratios (HRs) by ethnicity, SEP, and rural residency when adjusted for age and either FIGO or SEER code. The FIGO codes (Benedet *et al*, 2006) were, therefore, chosen as the classification for stage at diagnosis to be used in the analyses because they were recorded in the largest number of registrations.

To provide sufficient numbers in each category, the FIGO stage was grouped into four categories: 1, stages 0-IB2; 2, II-IIB; 3, III-IIIB; 4, IVA-IVB. A fifth category of 'missing' was utilised for cases where the FIGO stage was unknown. We conducted a basic sensitivity analysis to assess the potential for bias resulting from the exclusion of the women with missing stage data; this involved three sets of analyses: (i) adjusting for stage and excluding the women with missing stage data; (ii) including the women with and without missing stage data, and adjusting for stage with a dummy variable representing the women with missing stage data; and (iii) including the women with and without missing stage data, but not adjusting for stage. The three sets of analyses yielded the same patterns. We therefore present here the findings from the first method

(*i.e.* excluding women with missing stage), because it is necessary to adjust for stage, and this is the only approach that enables us to do this validly (Brewer *et al*, 2010; Brewer *et al*, 2009). Multiple imputation was not considered to be appropriate because of the additional assumptions on which it is based and the potential for introducing further bias (Greenland and Finkle, 1995). In some analyses, the FIGO stage was also further grouped into early stage (FIGO stages 0-IB2), which corresponds to the SEER summary stage of localised only, and late stage (FIGO stages II-IVB), which corresponds to the SEER regional or invasive carcinoma stages (Young *et al*, 2001).

Women whose cancer was registered on the day of their death (and who were, therefore, assumed to have a death-certificate-only registration), or who could not be allocated a deprivation score were excluded from the analyses. For Cox regression analyses, women were censored at the time of their death or on 31 December 2005 if they were still alive at that time.

All analyses were conducted using Intercooled Stata 8.2 for Windows (StataCorp, College Station, Texas, USA). In the preliminary analyses, logistic regression was used to determine if SEP (as estimated by NZDep2001), rural residency, or ethnicity were independently associated with stage at diagnosis. The Cox proportional hazards model (Cox, 1972) was then used to estimate the HRs of cervical cancer death associated with ethnicity, SEP, and rural residency. The models were run initially with each demographic factor being considered alone (adjusted for age and registration year as continuous variables), and then additionally adjusted for stage, and, finally, also being adjusted for the other demographic variables under consideration.

Results

Between January 1994 and June 2005, 2,260 cases of cervical cancer were registered on the NZCR. The following exclusions were made; 17 women because their cancer registration was made on the date of the woman's death, 124 cases because they did not have a domicile code that could be assigned an NZDep2001 score, and 525 because they did not have a FIGO code, leaving 1,594 women to be included in the analyses. Of these, 99.2% were diagnosed based on histology of the primary malignant tumour, 0.2% on histology of metastases, 0.3% on cytology and 0.4% on clinical investigation.

Twenty-three per cent (366) of the cases died from cervical cancer during the follow-up period; 74% (271) of these women were diagnosed with late-stage disease. Length of follow-up ranged from 11 days to 12 years, with a mean of five years. A further 5% (84) of cases died from causes other than cervical cancer, and their follow-up was censored on their date of death.

Table 2.1 shows the characteristics of the 1,594 women included in the analyses. The majority (73%) of the women were of 'Other' (99.7% European) ethnicity, which included two (0.1%) women with missing ethnicity data and three (0.2%) women who identified as 'African' (or cultural group of African origin).The women were aged 17–93 years (mean 48 years), with more than two thirds being diagnosed with cervical cancer before the age of 55. Most women (68%) were diagnosed at an early stage, with only 3% being diagnosed at the most advanced stage (stage IV). Twenty-eight per cent lived in the most-deprived NZDep2001 quintile areas in New Zealand, and 14% lived in the least-deprived areas. Only 9% of the women lived in a rural area.

Table 2.1. Characteristics of women diagnosed with cervical cancer in New Zealand, 1994-June 2005

Characteristic	*Number*	*%*
Ethnicity		
Other	1,163	73.0
Māori	292	18.3
Pacific	59	3.7
Asian	80	5.0
Age, years		
15–24	28	1.8
25–34	304	19.1
35–44	440	27.6
45–54	335	21.0
55–64	200	12.6
65–74	175	11.0
75–84	92	5.8
≥85	20	1.3
FIGO stage		
0–IB2	1,083	67.9
II–IIB	242	15.2
III–IIIB	219	13.7
IVA–IVB	50	3.1
NZDep2001, quintiles		
1 (Least deprived)	220	13.8
2	233	14.6
3	304	19.1
4	386	24.2
5 (Most deprived)	451	28.3
Urban/rural		
Main urban	1,194	74.9
Secondary urban	253	15.9
Rural	147	9.2
Registration year		
1994	140	8.8
1995	121	7.6
1996	149	9.4
1997	134	8.4
1998	154	9.7
1999	167	10.5
2000	174	10.9
2001	164	10.3
2002	145	9.1
2003	107	6.7
2004	103	6.5
2005 (to June 30)	36	2.3

FIGO: International Federation of Gynecology and Obstetrics;
NZDep2001: New Zealand Deprivation Index 2001.

Table 2.2 shows the distribution of stage at diagnosis by ethnicity, SEP, and urban/rural residency. The majority of women of all ethnicities were diagnosed with early-stage (FIGO stages 0-IB2) disease. Māori women (41.4%), however, were more often diagnosed with late-stage cervical cancer (FIGO stages II-IVB) compared to Pacific (32.2%), Asian (32.5%) and 'Other' (29.7%) women. Stage at diagnosis also differed by SEP, with women living in NZDep2001 quintile 1 (least deprived) being less frequently diagnosed (27.3%) at a late stage than women living in NZDep2001 quintile 5 (most deprived, 34.4%). Women living in a main (32.0%) or secondary (34.8%) urban area were more likely to have been diagnosed at a late stage than women living in a rural area (27.9%). The differences in stage at diagnosis by ethnicity were statistically significant (p=0.02), while those by deprivation (p=0.25) and by urban/rural residency (p=0.71) were not.

Logistic regression was used to examine the odds ratio (OR) of a late stage compared with an early stage at diagnosis (Table 2.2). Māori women (OR 2.75, 95% confidence interval 2.04-3.70) were considerably more likely to be diagnosed at a late stage compared to 'Other' women. Pacific women (1.38, 0.76-2.49) appeared to follow the same pattern (although the result was not statistically significant), but there was no evidence that Asian women (1.05, 0.62-1.77) were diagnosed later than 'Other' women. Compared with women living in areas with the lowest level of deprivation, women in the highest deprivation areas were more likely to be diagnosed at a late stage (1.52, 1.03-2.25). There was little evidence that women in secondary urban areas (1.09, 0.80-1.50) or women in rural areas (1.02, 0.67-1.53) were more likely than women living in main urban areas to be diagnosed at a late stage. When the individual demographic variables were also adjusted for each other, the ethnic differences remained largely

unchanged, whereas the associations with area-based levels of deprivation largely disappeared.

Table 2.3 shows the HRs for mortality by ethnicity, SEP, urban/rural residency, and stage at diagnosis. Māori women had a high HR of 2.15 (1.68-2.75), and this excess risk reduced by about one-half to 1.62 (1.25-2.09) when adjusted for stage. Further adjustment for SEP and urban/rural residency produced only a small additional reduction in the HR to 1.56 (1.19-2.05). In contrast, the high HR for Pacific women (1.98, 1.25-3.13) remained basically unchanged when adjusted for stage (1.96, 1.23-3.12) and when adjusted for the other demographic variables (1.95, 1.21-3.13). Asian women had a lower HR (0.81, 0.47-1.42), but this also did not substantially change when adjusted for stage (0.70, 0.40-1.23) or the other demographic variables (0.72, 0.41-1.27).

There were also relatively strong SEP differences in HRs, with women in the most deprived areas having a HR of 1.58 (1.10-2.28) compared with those in the lowest level of deprivation. In general, these HRs only changed a small amount when adjusted for stage at diagnosis but reduced more substantially when adjusted for ethnicity and urban/rural residency. The main determinant of this reduction in the HR was ethnicity. For example, the HR for quintile 5 reduced from 1.58 (1.10-2.28) to 1.38 (0.95-2.00) when adjusted for stage (Table 2.3), then only reduced to 1.35 (0.93-1.96) when adjusted for urban/rural residency, but reduced further to 1.13 (0.77-1.68) when adjusted for ethnicity (not shown in Table 2.3).

Table 2.2. Stage at diagnosis by ethnicity, socio-economic position and urban/rural residency

	FIGO stage at diagnosis, n (%)				*Odds ratios (OR) for late stage diagnosis (stage II-IV)* versus *early stage diagnosis (0-IB2)*	
	0-IB2	*II-IIB*	*III-IIIB*	*IVA-IVB*	*OR (95% confidence intervals) adjusted for age and registration year*	*OR (95% confidence intervals) adjusted for age, registration year and other variables in table*
Ethnicity						
Other	818 (70.3)	172 (14.8)	142 (12.2)	31 (2.7)	1.00[a]	1.00[a]
Māori	171 (58.6)	52 (17.8)	57 (19.5)	12 (4.1)	2.75 (2.04-3.70)	2.72 (1.98-3.73)
Pacific	40 (67.8)	9 (15.3)	7 (11.9)	3 (5.1)	1.38 (0.76-2.49)	1.38 (0.76-2.53)
Asian	54 (67.5)	9 (11.3)	13 (16.3)	4 (5.0)	1.05 (0.62-1.77)	1.07 (0.63-1.81)
NZDep2001, quintiles						
1 (Least deprived)	160 (72.7)	32 (14.5)	26 (11.8)	2 (0.9)	1.00[a]	1.00[a]
2	172 (73.8)	32 (13.7)	23 (9.9)	6 (2.6)	0.94 (0.60-1.49)	0.90 (0.57-1.44)
3	205 (67.4)	46 (15.1)	41 (13.5)	12 (3.9)	1.36 (0.89-2.07)	1.24 (0.81-1.91)
4	250 (64.8)	64 (16.6)	61 (15.8)	11 (2.8)	1.41 (0.95-2.11)	1.26 (0.84-1.90)
5 (Most deprived)	296 (65.6)	68 (15.1)	68 (15.1)	19 (4.2)	1.52 (1.03-2.25)	1.10 (0.73-1.66)
Urban/rural residency						
Main urban	812 (68.0)	185 (15.5)	163 (13.7)	34 (2.8)	1.00[a]	1.00[a]
Secondary urban	165 (65.2)	38 (15.0)	39 (15.4)	11 (4.3)	1.09 (0.80-1.50)	0.97 (0.70-1.34)
Rural	106 (72.1)	19 (12.9)	17 (11.6)	5 (3.4)	1.02 (0.67-1.53)	0.97 (0.64-1.48)

FIGO: International Federation of Gynecology and Obstetrics; NZDep2001: New Zealand Deprivation Index 2001. [a]Reference category.

Table 2.3. Hazard ratios (HRs) for mortality by ethnicity, socio-economic position, urban/rural residency, and stage at diagnosis

	Number of deaths	*Median survival time (years)*	*HR (95% confidence intervals (95% CI)) adjusted for age and registration year*	*HR (95% CI) adjusted for age, registration year and stage*	*HR (95% CI) adjusted for age, registration year, stage and other variables in table*
Ethnicity					
Other	241	4.82	1.00[a]	1.00[a]	1.00[a]
Māori	92	3.98	2.15 (1.68-2.75)	1.62 (1.25-2.09)	1.56 (1.19-2.05)
Pacific	20	4.03	1.98 (1.25-3.13)	1.96 (1.23-3.12)	1.95 (1.21-3.13)
Asian	13	5.51	0.81 (0.47-1.42)	0.70 (0.40-1.23)	0.72 (0.41-1.27)
Stage at diagnosis					
0–IB2	95	5.51	1.00[a]	1.00[a]	1.00[a]
II–IIB	92	3.45	4.60 (3.40-6.21)	4.60 (3.40-6.21)	4.15 (3.06-5.63)
III–IIIB	136	1.38	11.06 (8.31-14.71)	11.06 (8.31-14.71)	10.32 (7.73-13.77)
IVA–IVB	43	0.60	25.75 (17.82-37.22)	25.75 (17.82-37.22)	23.96 (16.53-34.73)
NZDep2001, quintiles					
1 (Least deprived)	38	4.96	1.00[a]	1.00[a]	1.00[a]
2	41	4.67	1.00 (0.64-1.55)	1.00 (0.64-1.55)	0.95 (0.61-1.48)
3	75	4.10	1.59 (1.08-2.35)	1.38 (0.93-2.05)	1.28 (0.86-1.91)
4	95	4.73	1.43 (0.98-2.08)	1.21 (0.83-1.77)	1.11 (0.76-1.64)
5 (Most deprived)	117	4.76	1.58 (1.10-2.28)	1.38 (0.95-2.00)	1.13 (0.77-1.68)
Urban/rural residency					
Main urban	268	4.61	1.00[a]	1.00[a]	1.00[a]
Secondary urban	68	4.63	1.24 (0.95-1.62)	1.21 (0.93-1.59)	1.14 (0.87-1.50)
Rural	30	5.02	1.03 (0.70-1.50)	1.19 (0.81-1.74)	1.11 (0.75-1.64)

NZDep2001: New Zealand Deprivation Index 2001. [a]Reference category.

Women living in secondary urban areas had a higher HR (1.24, 0.95-1.62) than women living in a main urban (reference category) or rural area (1.03, 0.70-1.50), but this excess risk largely disappeared when adjusted for ethnicity and SEP. The HR for secondary urban areas reduced from 1.24 (0.95-1.62) to 1.21 (0.93-1.59) when adjusted for stage (Table 2.3), then reduced to 1.19 (0.91-1.55) when adjusted for deprivation, and reduced further to 1.14 (0.87-1.50) when adjusted for ethnicity. For women living in a rural area, adjustment for stage increased the HR to 1.19 (0.81-1.74), adjustment for deprivation leaving the HR unchanged at 1.19 (0.81-1.75), and further adjustment for ethnicity reducing the HR to 1.11 (0.75-1.64).

Table 2.4 shows the same analyses as in Table 2.3 conducted separately in those diagnosed at an early stage and those diagnosed at a late stage. In general, the demographic differences in survival were slightly stronger in cases that were diagnosed at an early stage than in those diagnosed at a late stage, but the HRs were not substantially different between the two groups of cases, and the small observed differences were not statistically significant.

As the strongest differences were observed for ethnicity, the patterns by ethnicity were investigated further to assess whether they differed by time period of cancer diagnosis. HRs for each ethnic group were calculated for three four-year periods (1994-1997, 1998-2001 and 2002-2005) by stage at diagnosis, SEP, and urban/rural residency (Table 2.5). The ethnic-specific HRs differed significantly by time period of diagnosis (test for interaction for the findings in the third column of Table 2.5, $p<0.01$). For cases diagnosed during 1994-1997, Māori women (compared with 'Other' women) had an age and registration year adjusted HR of 2.34 (1.68-3.27), which reduced to 1.83 (1.29-

2.60) when it was adjusted for stage at diagnosis, and changed little when also adjusted for SEP and urban/rural residency. In contrast, for cases diagnosed during 1998-2001, stage at diagnosis accounted for a larger proportion of the excess risk in Māori women: the age and registration year adjusted HR of 2.01 (1.29-3.12) reduced to 1.25 (0.79-1.98) when it was adjusted for stage at diagnosis, and further reduced to 1.09 (0.67-1.79) when adjusted for SEP and urban/rural residency. For cases diagnosed during 2002-2005, stage at diagnosis accounted for almost all of the excess relative risk (RR) in Māori women: age and registration year adjusted HR 1.54 (0.75-3.13), age, registration year, and stage adjusted HR 0.90 (0.43-1.89), and age, registration year, stage, SEP, and urban/rural residency adjusted HR 0.82 (0.35-1.92). In contrast, adjustment for stage at diagnosis made little difference to the HRs for Pacific and Asian women in each time period, but the numbers involved were relatively small and the confidence intervals were correspondingly wide.

Table 2.4. Hazard ratios (HRs) for mortality by ethnicity, socio-economic position, urban/rural residency and stage at diagnosis[a]

	Number of deaths	*Early stage HR (95% confidence intervals)*	*Number of deaths*	*Late stage HR (95% confidence intervals)*
Ethnicity				
Other	64	1.00[b]	177	1.00[b]
Māori	20	1.73 (1.01-2.97)	72	1.46 (1.06-2.01)
Pacific	8	2.76 (1.29-5.95)	12	1.56 (0.85-2.87)
Asian	3	0.79 (0.25-2.53)	10	0.71 (0.37-1.37)
NZDep2001, quintiles				
1 (Least deprived)	10	1.00[b]	28	1.00[b]
2	13	1.16 (0.51-2.65)	28	0.87 (0.51-1.48)
3	17	1.27 (0.58-2.80)	58	1.22 (0.76-1.95)
4	24	1.22 (0.57-2.58)	71	1.04 (0.66-1.64)
5 (Most deprived)	31	1.18 (0.56-2.48)	86	1.07 (0.67-1.70)
Urban/rural residency				
Main urban	66	1.00[b]	202	1.00[b]
Secondary urban	22	1.51 (0.91-2.48)	46	1.02 (0.73-1.42)
Rural	7	0.85 (0.39-1.87)	23	1.26 (0.79-1.98)

[a]All analyses were adjusted for age, registration year and the other variables listed in the table. The analyses for late stage cervical cancer cases were also adjusted for stage (II, III, or IV); [b]Reference category.
NZDep2001: New Zealand Deprivation Index 2001.

Table 2.5. Hazard ratios (HRs) for mortality by ethnicity, stage at diagnosis, socio-economic position, urban/rural residency and time period

	Number of deaths	*HR (95% confidence intervals (CI)) adjusted for age and registration year*	*HR (95% CI) adjusted for age, registration year and stage*	*HR (95% CI) adjusted for age, registration year, stage and other variables*[a]
1994-1997				
Ethnicity				
Other	111	1.00[b]	1.00[b]	1.00[b]
Māori	54	2.34 (1.68-3.27)	1.83 (1.29-2.60)	1.90 (1.29-2.79)
Pacific	9	1.51 (0.76-2.98)	1.50 (0.74-3.01)	1.76 (0.85-3.64)
Asian	2	0.29 (0.07-1.17)	0.23 (0.06-0.95)	0.25 (0.06-1.02)
1998-2001				
Ethnicity				
Other	96	1.00[b]	1.00[b]	1.00[b]
Māori	28	2.01 (1.29-3.12)	1.25 (0.79-1.98)	1.09 (0.67-1.79)
Pacific	5	1.85 (0.75-4.56)	1.78 (0.72-4.40)	1.37 (0.53-3.50)
Asian	9	1.57 (0.79-3.12)	1.39 (0.70-2.76)	1.28 (0.64-2.56)
2002-2005				
Ethnicity				
Other	34	1.00[b]	1.00[b]	1.00[b]
Māori	10	1.54 (0.75-3.13)	0.90 (0.43-1.89)	0.82 (0.35-1.92)
Pacific	6	3.49 (1.45-8.42)	5.56 (2.22-13.94)	5.15 (1.89-14.03)
Asian	2	0.61 (0.15-2.57)	0.56 (0.13-2.38)	0.77 (0.18-3.37)

[a]Other variables were socio-economic position and urban/rural residency; [b]Reference category.

Discussion

This study found that there are major ethnic differences in cervical cancer survival in New Zealand, particularly between Māori and the 'Other' (predominantly European) ethnic group, which are partly explained by differences in stage at diagnosis but which are not explained to any significant extent by area-based SEP or urban/rural residency. In contrast, the high death rate in Pacific women's cervical cancer cases remained virtually unchanged when adjusted for stage at diagnosis, and there was a small non-significantly reduced risk in Asian cases. The socio-economic differences in survival were only of moderate strength and largely disappeared when adjusted for ethnicity, while the urban/rural differences in survival were relatively small.

A new finding of this study is that the magnitude of the Māori/non-Māori differences and the importance of stage at diagnosis as an explanation for the higher death rate in Māori women have changed over time (Table 2.5). These findings are largely consistent with evidence that (1) Māori/non-Māori inequalities in life expectancy widened during the 1990s, when general socio-economic inequalities in New Zealand increased, and that widening inequalities in cancer mortality accounted for a substantial proportion of this trend (Ajwani *et al*, 2003b), and (2) the Māori/non-Māori differences began to stabilise or even decrease in the late 1990s (Blakely *et al*, 2007). With regard to the specific findings for cervical cancer mortality reported here, in the earliest time period that was investigated (1994-1997), about one half of the excess mortality in Māori women was due to stage at diagnosis, but one half was not, indicating that both pre-diagnostic and post-diagnostic factors were playing an important role. By the latest time period examined (2002-2005), the Māori excess mortality had decreased, and stage at

diagnosis accounted for all of the remaining excess mortality risk in Māori women, indicating that in more recent times pre-diagnostic factors have become relatively more important. These pre-diagnostic factors may include differences in screening rates and also in the timeliness of follow-up and subsequent treatment (of pre-malignant changes) of women with an abnormal cervical cytology result (Brewer *et al*, 2008b). In Pacific women, however, stage at diagnosis was associated with only a small amount of the survival differences in each time period, a finding which is consistent with the stage distribution (Table 2.2) in Pacific women not being very different to that in 'Other' women. The excess risk in Pacific women is, therefore, not due to stage at diagnosis, but is likely to be due to post-diagnosis factors, such as access to and uptake of treatment.

Internationally, ethnicity has consistently been shown to be a risk factor for late stage cervical cancer diagnosis (Condon *et al*, 2005; Eggleston *et al*, 2006), and in New Zealand, it has been shown that Māori women are more likely than non-Māori women to be diagnosed with cervical cancer at a late stage (Robson and Harris, 2007; Sadler *et al*, 2004). The results of the current study confirm these findings, suggesting that Māori women are more likely to be diagnosed at a late stage, independent of SEP and urban/rural residency. Similar findings have previously been reported for other cancers (Haynes *et al*, 2008; Sneyd, 2008).

Although there have been no previously published New Zealand studies of the effect of urban/rural residency on cervical cancer survival, studies on survival of cancer of the colorectum and anus, trachea, bronchus and lung, breast, prostate, melanoma (Haynes *et al*, 2008), upper gastrointestine (Gill and Martin, 2002), and breast (Bennett *et al*, 2007)

in New Zealand have shown that geographic location has only a small effect on survival. SEP, as estimated by an area-based composite score (NZDep2001), gave only moderately strong findings, which decreased slightly with adjustment for stage at diagnosis but decreased substantially when adjusted for ethnicity and urban/rural residency. As noted, most of this change was due to the adjustment for ethnicity. Conversely, as the findings by ethnicity hardly changed when they were adjusted for SEP and urban/rural residency, ethnicity was not confounded by SEP.

What could explain these findings? They are very unlikely to be due to biological or genetic differences (Dachs *et al*, 2008) because these generally only have a very weak association with ethnicity (Pearce *et al*, 2004), a concept which incorporates biology but also includes a wide variety of historical, cultural, and lifestyle factors (Durie, 1995). It is already well-established that there are major ethnic differences in access to and uptake of cervical cancer screening in New Zealand (Brewer *et al*, 2008b). These appear to account for about one half of the increased mortality in Māori cervical cancer cases in the 1990s but almost all of the Māori excess mortality in the more recent time period (2002-2005), although other pre-diagnostic factors may also play a role. The rest of the excess Māori mortality during the 1990s and virtually all of the excess Pacific mortality throughout the entire time period (1994-2005) appear to be due to post-diagnostic factors. One obvious possibility is the previously documented ethnic differences in access to healthcare in New Zealand (Cormack *et al*, 2005; Ellison-Loschmann and Pearce, 2006; Tobias and Yeh, 2007). Studies in the United States have found that the quality of cancer treatment differs by ethnicity (Smedley *et al*, 2002), and it is possible that this is also the case in New Zealand (although the authors are not aware of any specific studies of this in New Zealand). It should be noted that a higher number of

comorbid conditions in Māori and Pacific women could also limit treatment and post-treatment options (Jeffreys *et al*, 2005b), but it is currently unclear as to what proportion of the ethnic differences is accounted for by such comorbid conditions.

The strengths and limitations of this study should be acknowledged. A strength of the study is that the Cancer Registry Act came into effect in 1994, making cancer registration mandatory (Ministry of Health, 2008a), and case under-ascertainment is, therefore, unlikely (Ministry of Health, 2002). Death registration is also mandatory in New Zealand and can be linked to cancer registrations using the NHI number; thus, it is very likely that all of the cases that died in New Zealand were identified. On the other hand, cases that died overseas would not have been identified, and this may particularly apply to Pacific cases who in some instances may have returned to the Pacific following a cervical cancer diagnosis. However, this would have produced an under-estimation of the death rate in Pacific cases and, therefore, could not explain the increased risks seen in this ethnic group.

There may have been some misclassification of cause of death, but this is unlikely to have been major or to have varied significantly by ethnicity because the analyses were restricted to cases that had been registered prior to death. Furthermore, in cases that are registered prior to death, information from the NZCR is used to classify the underlying cause of death (New Zealand Health Information Service, 2004); misclassification of a cervical cancer death is, therefore, unlikely. The fact that only 73% of cases had a FIGO code recorded could introduce selection bias, but a previous analysis found that there was little difference in overall cancer survival between those with stage data and those without stage data (Jeffreys *et al*, 2005b). It is also possible that there was residual

confounding from inaccuracies in stage classification, as there were not sufficient numbers to adjust for more detailed stage at diagnosis. Thus, residual confounding by stage could explain some of the results. However, the fact that the Māori/'Other' differences almost completely disappeared when the analyses were adjusted for stage indicates that this is not likely to be a serious source of bias.

Other possible limitations of the study include the potential misclassification of ethnicity, which has been estimated as a 17% undercount of Māori cancer registrations (Cormack *et al*, 2005) (this involves misclassification on ethnicity on registrations rather than case under-ascertainment). Thus, the 'Other' ethnic group may contain some Māori cases that were incorrectly classified, thereby diluting the ethnic survival differences. As noted above, the classification of ethnicity was based on the wording of the corresponding Census questions, and these have changed over time; once again, however, this is unlikely to have produced serious bias because the ethnicity recorded on the NZCR was also used to classify the corresponding deaths, and the analyses were adjusted for registration year.

There may also be misclassification of area-based SEP and urban/rural residency in cancer registrations, but in each instance, any such misclassification is unlikely to be associated with subsequent survival and, if anything, is likely to produce underestimates of the differences in survival between these various demographic groups. Furthermore, the methods used in this study are standard and have shown strong SEP differences for many other health problems (Haynes *et al*, 2008; McFadden *et al*, 2004; Metcalf *et al*, 2008; Robson and Harris, 2007; Tobias and Yeh, 2007). It is, therefore, unlikely that the methods used account for the relative lack of SEP differences found in the current

study. The final limitation of the study is that the NZCR and Mortality Collection do not include information on comorbid conditions, treatment, or other related factors that may explain some of the survival differences found in this study, and this information, therefore, could not be included in the analyses. However, the lack of this information does not represent a bias in the findings presented but rather would have been useful in terms of interpreting the reasons for the observed differences.

These initial analyses of inequalities in cervical cancer survival in New Zealand provide timely baseline data. New Zealand commenced a vaccination programme with Gardasil (Merck, Auckland, NZ) in September 2008, which will provide vaccinated women with immunity to human papillomavirus (HPV) subtypes 16, 18, 6 and 11. However, subtypes 16 and 18 are estimated to only account for about 70% of current cervical cancer cases (the exact figure is unknown because a national HPV prevalence survey has not been done). Furthermore, the vaccine will not yield major benefits for several decades, and the duration of protection provided by the vaccine is currently unknown. It is as yet not known what the uptake of the vaccine will be across various demographic groups and, thus, whether, for example, it will increase or decrease the relative inequalities by ethnicity in cervical cancer incidence, mortality and survival.

Conclusions

This study has found that there are major ethnic differences in cervical cancer survival, which are in part explained by differences in stage at diagnosis. After adjustment for stage at diagnosis, Māori ethnicity was still a major determinant of cervical cancer survival in 1994-1997 but not in later years. Survival was worse for Pacific cases for all

three time periods, but the numbers were relatively small. SEP and urban/rural residency had only relatively weak independent associations with survival. Thus, for the earlier time period (1994-1997), both pre-diagnostic and post-diagnostic factors contributed to the Māori/'Other' differences in survival, whereas in the later time period (2002-2005) the differences were almost entirely due to pre-diagnostic factors. In contrast, the corresponding analyses for Pacific cases indicated that post-diagnostic factors remain important, even in the most recent time period. These findings of past differences warrant further investigation, including consideration of data on screening history, comorbid conditions, and access to cancer treatment.

CHAPTER 3

Does screening history explain the ethnic differences in stage at diagnosis of cervical cancer in New Zealand?

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Background: There are ethnic disparities in cervical cancer survival in New Zealand. The objectives of this study were to assess the associations of screening history, ethnicity, socio-economic position and rural residency with stage at diagnosis in women diagnosed with cervical cancer in New Zealand during 1994-2005.

Methods: The 2,323 cases were categorised as 'ever screened' if they had had at least one smear prior to six months before diagnosis, and as 'regular screening' if they had had no more than 36 months between any two smears in the period 6-114 months before diagnosis. Logistic regression was used to estimate the associations of screening history, ethnicity, socio-economic position and urban/rural residency with stage at diagnosis.

Results: The percentages 'ever screened' were 43.3% overall, 24.8% in Pacific, 30.5% in Asian, 40.6% in Māori, and 46.1% in 'Other' women. The corresponding estimates for 'regular screening' were 14.0, 5.7, 7.8, 12.5 and 15.3%. Women with 'regular screening' had a lower risk of late-stage diagnosis (odds ratio 0.16, 95% confidence intervals 0.10-0.26), and the effect was greater for squamous cell carcinoma (0.12, 0.07-0.23) than for adenocarcinoma (0.32, 0.13-0.82). The increased risk of late-stage diagnosis (2.72, 1.99-3.72) in Māori (compared with 'Other') women decreased only slightly when adjusted for screening history (2.45, 1.77-3.39).

Conclusions: Over half of cases had not been 'ever screened'. Regular screening substantially lowered the risk of being diagnosed at a late stage. However, screening history does not appear to explain the ethnic differences in stage at diagnosis.

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Introduction

In 2005, cervical cancer was the ninth most common site of cancer registration for New Zealand females (Ministry of Health, 2008a; Ministry of Health, 2009a), and the incidence and mortality rates were moderately high compared with the rest of the developed world (The Descriptive Epidemiology Group of IARC, 2002). Over the last decade, New Zealand's rates of cervical cancer have been decreasing (Brewer *et al*, 2008b; National Cervical Screening Programme, 2005), with the data for 2005 showing an age-adjusted incidence rate of 6.2 and an age-adjusted mortality rate of 1.9 per 100,000 women of all ages (Ministry of Health, 2009a). The most likely reason for these decreases is the establishment in 1990-91 of the New Zealand National Cervical Screening Programme (NCSP) (Paul *et al*, 2005). The NCSP recommends that all women aged 20-69 years have a cervical cytology test once every three years (National Screening Unit, 2008).

However, incidence and mortality rates are not the same across ethnic groups within New Zealand. For example, in 2005, Māori women had an incidence rate of 9.0, Pacific women 16.3 and 'Other' (predominantly European) women 5.6 per 100,000 women; Māori women had a mortality rate of 6.5, Pacific women 7.1 and 'Other' women 1.4 per 100,000 women (Ministry of Health, 2009a). The current authors have previously reported demographic differences in cervical cancer survival in New Zealand (Brewer *et al*, 2009). Māori and Pacific women had higher death rates than 'Other' women, whereas Asian women had a lower risk. Adjustment for stage at diagnosis explained some of the increased risk in Māori women (compared with 'Other' women), but only

very little of the differences in Pacific or Asian women. Socio-economic position (SEP) and urban/rural residency had only marginal effects.

One possible explanation for these differences is that rates of cervical screening also differ across the ethnic groups in New Zealand. In 2006, the coverage (had a cytology or histology result recorded on the NCSP-Register (NCSP-R) in the previous three years) rates were 46.6% for Māori women, 43.9% for Pacific women, and 75.7% for 'Other' women (Brewer *et al*, 2008b). As part of the ongoing work to monitor and improve the NCSP, an audit of the screening histories of women diagnosed with invasive cervical cancer between 1 January 2000 and 30 September 2002 was undertaken (Sadler *et al*, 2004). The aims of the Audit included providing information to contribute to the elimination of the ethnic disparities in the incidence of and mortality from invasive cervical cancer. The Audit found that only 50% of the women had had a smear in the 6-42 months prior to diagnosis (a three-year period) and that only 20% of the women had an adequate screening history (no interval of more than three years between screening smears in the six months to seven years prior to diagnosis). The Audit also found that more Māori than non-Māori women had late stage disease (International Federation of Gynecology and Obstetrics (FIGO) (Benedet *et al*, 2006) stage 2+) at diagnosis and that "there was an impression that at all steps of the screening pathway, Māori women were less well served [than non-Māori women]" (Sadler *et al*, 2004).

The current study therefore investigated the screening history of women diagnosed with cervical cancer in New Zealand during 1994-2005, to examine the associations of

screening history with stage at diagnosis, and whether differences in screening history explain the ethnic, socio-economic and urban/rural differences in stage at diagnosis.

Methods

The source population comprised all cervical cancer cases registered with the New Zealand Cancer Registry (NZCR) between 1 January 1994 and 31 December 2005. The NZCR records self-identified ethnicity, where people may record multiple responses. Participants who reported more than one ethnicity were classified into a single ethnicity using a standard system of prioritisation: Māori>Pacific>Asian>'Other' (New Zealand Department of Statistics, 1990). Participants with missing ethnicity data were included in the 'Other' (predominantly European) ethnic group in the analyses. This approach is standard practice in New Zealand health research (Ministry of Health, 2002; Ministry of Health, 2006).

SEP was estimated using the New Zealand Deprivation Index 2001 (NZDep2001) (Crampton *et al*, 2004). Each participant was assigned a score based upon the residential area (the domicile code) in which they lived as recorded on the NZCR at the time of registration. These scores were then grouped into quintiles, with a value of five indicating that the area is in the most deprived 20% of small areas in New Zealand (Crampton *et al*, 2004).

The domicile code recorded for each participant was also used to assign urban/rural residency according to population size (Statistics New Zealand, 2008). Participants were classified as living in a main urban area (with a population of ≥30,000), a

secondary or minor urban area (population ≥1,000 to 29,999), or a rural area (population <1,000).

The FIGO (Benedet *et al*, 2006) stage at diagnosis was obtained from the NZCR. FIGO codes were used in these analyses because they were available for a greater number of registrations (74%) than the other staging systems recorded on the NZCR (Brewer *et al*, 2009). There was little ethnic difference in the percentage of cases with missing FIGO codes: 24% of Māori, 32% of Pacific, 33% of Asian and 26% of 'Other' cases had missing FIGO codes. Similarly, the percentages of cases with missing FIGO codes in each of the five quintiles of NZDep2001 were as follows: 25, 28, 26, 26, and 26.

The FIGO stages were grouped into early stage (FIGO stages 0-IB2), which corresponds to the SEER summary stage of localised only, and late stage (FIGO stages II-IVB), which corresponds to the SEER regional or invasive carcinoma stages (Young *et al*, 2001). Women with an unknown stage at diagnosis, or who could not be allocated a deprivation score, were excluded from the analyses.

Each cervical cancer case was categorised by histological type according to the International Classification of Diseases for Oncology (ICD-O) (Fritz *et al*, 2000) code assigned by the NZCR, as follows: adenocarcinoma (ICD-O codes 8140-8550), adenosquamous cell carcinoma (ICD-O codes 8560, 8570), squamous cell carcinoma (ICD-O codes 8050-8082), other histological types (ICD-O codes 8800-8932, 8990-8991, 9040-9044, 9120-9134 and 9540-9581) and cervical cancer not otherwise specified (NOS; ICD-O codes 8000-8004, 8010-8034, 9990) (Fritz *et al*, 2000; Health Canada, 2002; Vizcaino *et al*, 1998).

The National Health Index number (which uniquely identifies individual health care users) for each of the cervical cancer cases registered with the NZCR between 1994 and 2005 was used to obtain the woman's screening history from the NCSP-R. The NCSP-R is governed by the Health (National Cervical Screening Programme) Amendment Act, which came into effect in 2004, and stipulates that all cervical cytological and histological test results must be sent to the NCSP (for entry onto the NCSP-R), unless the woman chooses to withdraw her enrolment from the Programme (please see the '*Methodological issues and limitations*' section, page 137, for further information). The NCSP-R also holds basic demographic details about all enrolled women.

The classifications of screening history were based on those used for the New Zealand Cervical Cancer Audit (Sadler *et al*, 2004) and for quality monitoring by the NCSP (Ministry of Health, 2000). Women were categorised as 'not screened' or 'ever screened'. The former category included: 'no screening' (no cervical smears before diagnosis); and 'pre-diagnostic only' (one or more smears in the six months prior to diagnosis but not previously). The latter category included: 'irregular screening – participation' (one or more smears in the period 6-84 months before diagnosis); 'irregular screening – coverage' (one or more smears in the period 6-42 months before diagnosis); 'regular screening' (meeting the criteria for 'coverage' and with no more than 36 months between any two smears in the period 6-114 months before diagnosis); and, 'some screening' (one or more smears prior to six months before diagnosis), which described women that did not meet the criteria for the previous categories. Thus all women were categorised as either 'not screened' or 'ever screened', and then further sub-categorised into the aforementioned mutually exclusive categories. In New Zealand,

women are recommended to have a screening smear once every three years (36 months) (National Screening Unit, 2008), meaning that the period of time encompassed by the 'irregular screening – participation' category should include at least two smears, and the period of time for the 'irregular screening – coverage' category should include a previous smear from a woman who had screen detected cancer (where her 'diagnostic' smear was taken in the six months prior to diagnosis). The final category of 'regular screening' indicates that the woman did not have an interval between smears of more than the recommended three years at any time in the nine years prior to the six months before diagnosis. This time period allows for three screening cycles to have taken place. We excluded all of the smears taken in the six months immediately prior to diagnosis since some of these will have been taken for diagnostic, not screening, purposes (Sasieni *et al*, 2003; Spayne *et al*, 2007). Cervical screening guidelines are extremely complex (National Screening Unit, 2008), and the categories used in this study are therefore only able to approximate the women's screening histories (Sadler *et al*, 2004).

The New Zealand Central Ethics Committee granted ethical approval for the study.

All analyses were conducted using Intercooled Stata 10 for Windows (StataCorp, College Station, Texas, USA). Logistic regression was used to estimate whether the associations of screening history, ethnicity, SEP or rural residency were independently associated with stage at diagnosis.

Results

There were 2,323 cases of cervical cancer registered on the NZCR between 1 January 1994 and 31 December 2005, and all of these cases were included in the descriptive analyses of screening history (Table 3.1). Overall, more than half (56.7%) of the women had not had a screening smear. The percentages 'ever screened' and for 'regular screening' were highest in 'Other' women (46.1 and 15.3%, respectively), and lowest in Pacific women (24.8 and 5.7%, respectively). The percentages 'ever screened' also varied by age, peaking at 71.7% in women aged 25-34 years and then gradually decreasing to the lowest percentage (9.0%) in women aged ≥75 years. The percentage 'ever screened' was particularly low in women with squamous cell carcinoma (41.3%) or adenosquamous cell carcinoma (36.8%), compared with cases of adenocarcinoma (59.7%).

Screening rates increased over time (Table 3.1), with 29.5% of cases registered during 1994-1997 (*i.e.* during the early years of the screening programme) having been 'ever screened', 49.8% during 1998-2001 and 52.6% during 2002-2005.

In the analyses of risk factors for late-stage diagnosis (Tables 3.2 and 3.3), 621 women were excluded because they did not have a FIGO code. As noted above, these women had a similar ethnic and SEP distribution to the cases that did have a FIGO code. A further 77 cases were excluded because they did not have a domicile code that could be assigned an NZDep2001 score, leaving 1,625 women included in the analyses.

Table 3.2 shows the associations of screening history with stage at diagnosis by histological type. Compared with 'no screening smears', women with 'regular screening' had a lower risk of late-stage diagnosis (compared with early-stage diagnosis; odds ratio (OR) 0.16, 95% confidence intervals 0.10-0.26), and the effect appeared larger for squamous cell carcinoma (0.12, 0.07-0.23) than for adenocarcinoma (0.32, 0.13-0.82). Women who were in the categories 'irregular screening – coverage' (0.19, 0.13-0.29) and 'irregular screening – participation' (0.17, 0.10-0.31), also had lower ORs (compared with women with 'no screening smears'), but women in the 'some screening' category did not (0.81, 0.39-1.69). The decreased ORs in screened women were seen in all time periods (not shown in Table 3.2): for example, the ORs for 'regular screening' were 0.28 (0.12-0.68) in 1994-97, 0.13 (0.06-0.26) in 1998-2001 and 0.06 (0.01-0.21) in 2002-05.

Table 3.3 shows the associations of ethnicity, SEP and urban/rural residency with stage at diagnosis. In general, adjustment for screening history made little difference to the demographic differences in stage at diagnosis. In particular, the increased risk of a late-stage diagnosis for Māori women decreased only slightly (from 2.72 to 2.45) when adjusted for screening history. In contrast, the increased risk for a late-stage diagnosis for Pacific women (1.45) disappeared when adjusted for screening history (0.99). These findings were maintained when the analysis was repeated for the subgroup of women with squamous cell carcinoma (Table 3.3). However, there were quite different patterns for adenocarcinoma, with Māori, Pacific and Asian women showing increased risks of a late stage of diagnosis, which decreased only slightly when adjusted for screening history.

Table 3.1. Characteristics of women diagnosed with cervical cancer in New Zealand, 1994-2005

Characteristic	*Not screened*				*Ever screened*											
	No smears or only after diagnosis		*Smear only in 6 months prior to diagnosis*		*Some screening*		*Irregular screening - participation*		*Irregular screening - coverage*		*Regular screening*		*Total 'ever screened'*		*Total participants*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Total	511	22.0	807	34.7	57	2.5	198	8.5	426	18.3	324	14.0	1,005	43.3	2,323	100
Ethnicity																
Other	354	21.1	549	32.8	33	2.0	149	8.9	333	19.9	256	15.3	771	46.1	1,674	100
Māori	89	21.4	158	38.0	18	4.3	36	8.7	63	15.1	52	12.5	169	40.6	416	100
Pacific	42	40.0	37	35.2	5	4.8	5	4.8	10	9.5	6	5.7	26	24.8	105	100
Asian	26	20.3	63	49.2	1	0.8	8	6.3	20	15.6	10	7.8	39	30.5	128	100
Age (years)																
15-24	4	11.4	8	22.9	0	0.0	3	8.6	12	34.3	8	22.9	23	65.7	35	100
25-34	28	7.0	85	21.3	14	3.5	73	18.3	106	26.6	93	23.3	286	71.7	399	100
35-44	68	11.1	207	33.8	18	2.9	59	9.6	150	24.5	110	18.0	337	55.1	612	100
45-54	110	22.9	191	39.8	9	1.9	34	7.1	81	16.9	55	11.5	179	37.3	480	100
55-64	72	23.8	126	41.7	6	2.0	14	4.6	46	15.2	38	12.6	104	34.4	302	100
65-74	94	34.6	122	44.9	4	1.5	10	3.7	23	8.5	19	7.0	56	20.6	272	100
≥75	135	60.5	68	30.5	6	2.7	5	2.2	8	3.6	1	0.4	20	9.0	223	100
FIGO stage																
0-IB2	118	10.2	396	34.3	22	1.9	131	11.3	280	24.2	208	18.0	641	55.5	1,155	100
II-IIB	66	25.2	124	47.3	12	4.6	11	4.2	28	10.7	21	8.0	72	27.5	262	100
III-IIIB	112	48.3	76	32.8	6	2.6	11	4.7	19	8.2	8	3.4	44	19.0	232	100
IVA-IVB	26	49.1	19	35.8	2	3.8	0	0.0	4	7.5	2	3.8	8	15.1	53	100
Missing	189	30.4	192	30.9	15	2.4	45	7.2	95	15.3	85	13.7	240	38.6	621	100
Histological type																
Squamous cell carcinoma	338	19.8	663	38.9	43	2.5	153	9.0	291	17.1	217	12.7	704	41.3	1,705	100
Adenosquamous carcinoma	31	24.8	48	38.4	3	2.4	10	8.0	14	11.2	19	15.2	46	36.8	125	100
Adenocarcinoma	69	18.9	78	21.4	9	2.5	26	7.1	107	29.3	76	20.8	218	59.7	365	100

Table 3.1. (continued) Characteristics of women diagnosed with cervical cancer in New Zealand, 1994-2005

Characteristic	*Not screened*				*Ever screened*											
	No smears or only after diagnosis		*Smear only in 6 months prior to diagnosis*		*Some screening*		*Irregular screening - participation*		*Irregular screening - coverage*		*Regular screening*		*Total 'ever screened'*		*Total participants*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Histological type																
Other	5	20.8	6	25.0	1	4.2	4	16.7	3	12.5	5	20.8	13	54.2	24	100
Not otherwise specified	68	65.4	12	11.5	1	1.0	5	4.8	11	10.6	7	6.7	24	23.1	104	100
NZDep2001, quintiles																
1 (Least deprived)	57	19.1	98	32.9	7	2.3	33	11.1	57	19.1	46	15.4	143	48.0	298	100
2	66	19.8	115	34.5	1	0.3	24	7.2	76	22.8	51	15.3	152	45.6	333	100
3	100	24.0	125	30.0	13	3.1	30	7.2	83	20.0	65	15.6	191	45.9	416	100
4	119	22.6	201	38.2	15	2.9	46	8.7	87	16.5	58	11.0	206	39.2	526	100
5 (Most deprived)	138	22.2	211	33.9	20	3.2	56	9.0	107	17.2	91	14.6	274	44.0	623	100
Missing	31	24.4	57	44.9	1	0.8	9	7.1	16	12.6	13	10.2	39	30.7	127	100
Urban/rural																
Main urban	362	22.1	559	34.1	45	2.7	140	8.5	300	18.3	234	14.3	719	43.8	1,640	100
Secondary urban	79	21.9	134	37.1	7	1.9	31	8.6	65	18.0	45	12.5	148	41.0	361	100
Rural	39	19.9	58	29.6	4	2.0	18	9.2	45	23.0	32	16.3	99	50.5	196	100
Missing	31	24.6	56	44.4	1	0.8	9	7.1	16	12.7	13	10.3	39	31.0	126	100
Registration year																
1994-1997	220	26.1	374	44.4	0	0.0	23	2.7	121	14.4	105	12.5	249	29.5	843	100
1998-2001	156	19.1	253	31.0	18	2.2	83	10.2	161	19.8	144	17.7	406	49.8	815	100
2002-2005	135	20.3	180	27.1	39	5.9	92	13.8	144	21.7	75	11.3	350	52.6	665	100
Screened in 6 months prior																
Yes	0	0.0	807	49.1	42	2.6	176	10.7	349	21.2	270	16.4	837	50.9	1,644	100
No	511	75.3	0	0.0	15	2.2	22	3.2	77	11.3	54	8.0	168	24.7	679	100

FIGO: International Federation of Gynecology and Obstetrics; NZDep2001: New Zealand Deprivation Index 2001.

Table 3.2. Odds ratios (95% confidence intervals) for screening history and late-stage diagnosis (stages II-IV) *versus* early-stage diagnosis (stages 0-IB2)[a]

	Histological type		
Screening history	*All cases*	*Squamous cell carcinoma*	*Adenocarcinoma[b]*
No screening smears	1.00[c]	1.00[c]	1.00[c]
'Diagnostic' only	0.39 (0.28-0.53)	0.39 (0.28-0.56)	0.29 (0.13-0.66)
Some screening	0.81 (0.39-1.69)	0.78 (0.34-1.77)	1.46 (0.27-7.96)
Irregular - participation	0.17 (0.10-0.31)	0.16 (0.08-0.30)	0.28 (0.07-1.14)
Irregular - coverage	0.19 (0.13-0.29)	0.17 (0.10-0.28)	0.34 (0.14-0.84)
Regular	0.16 (0.10-0.26)	0.12 (0.07-0.23)	0.32 (0.13-0.82)

[a]Adjusted for age, registration year, ethnicity, NZDep2001, urban/rural residency. [b]Adenocarcinoma including adenosquamous carcinoma. [c]Reference category.

Table 3.3. Odds ratios (95% confidence intervals) for ethnicity, NZDep2001, urban/rural residency and late-stage diagnosis (stages II-IV) *versus* early-stage diagnosis (stages 0-IB2)

	All cases		*Squamous cell carcinoma*		*Adenocarcinoma*[a]	
	Adjusted for age, registration year and other variables in table	*Adjusted for age, registration year, other variables in table and screening history*	*Adjusted for age, registration year and other variables in table*	*Adjusted for age, registration year, other variables in table and screening history*	*Adjusted for age, registration year and other variables in table*	*Adjusted for age, registration year, other variables in table and screening history*
Ethnicity						
Other	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]
Māori	2.72 (1.99-3.72)	2.45 (1.77-3.39)	2.73 (1.93-3.88)	2.42 (1.68-3.49)	2.10 (0.96-4.57)	1.93 (0.86-4.33)
Pacific	1.45 (0.81-2.61)	0.99 (0.54-1.81)	1.44 (0.75-2.77)	0.95 (0.49-1.88)	2.51 (0.61-10.35)	2.26 (0.51-10.06)
Asian	1.00 (0.59-1.69)	0.92 (0.53-1.57)	0.73 (0.39-1.36)	0.69 (0.36-1.31)	2.81 (0.98-8.06)	2.62 (0.88-7.81)
NZDep2001, quintiles						
1 (Least deprived)	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]
2	0.89 (0.56-1.40)	0.88 (0.55-1.42)	0.87 (0.52-1.46)	0.88 (0.51-1.51)	0.90 (0.30-2.70)	1.00 (0.32-3.09)
3	1.27 (0.83-1.94)	1.24 (0.79-1.92)	1.19 (0.73-1.94)	1.21 (0.72-2.02)	1.83 (0.70-4.76)	1.83 (0.68-4.94)
4	1.26 (0.84-1.89)	1.22 (0.80-1.86)	1.16 (0.73-1.83)	1.21 (0.75-1.95)	1.91 (0.72-5.12)	1.82 (0.66-5.07)
5 (Most deprived)	1.10 (0.73-1.65)	1.11 (0.72-1.69)	1.00 (0.63-1.59)	1.06 (0.66-1.72)	1.73 (0.64-4.65)	1.82 (0.65-5.10)
Urban/rural residency						
Main urban	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]
Secondary urban	0.96 (0.69-1.33)	0.95 (0.67-1.33)	1.02 (0.71-1.46)	1.04 (0.72-1.53)	0.67 (0.28-1.57)	0.55 (0.22-1.35)
Rural	0.98 (0.65-1.50)	1.00 (0.65-1.55)	1.01 (0.63-1.61)	1.03 (0.63-1.68)	0.76 (0.25-2.36)	0.72 (0.22-2.36)

[a]Adenocarcinoma including adenosquamous carcinoma. [b]Reference category. NZDep2001: NZ Deprivation Index 2001.

Discussion

The general strengths and limitations of the data on which these new analyses are based have been described previously (Brewer *et al*, 2009), and we will therefore focus on factors related to the new findings that have been presented here, *i.e.* the screening histories. One of the strengths of the screening-history data is that all cervical smear results taken within New Zealand are required by law to be sent to the NCSP-R, and so for most women it is extremely unlikely that their screening histories are incomplete. However, women were able to 'opt-off' individual test results, and it is not clear how often this occurred, although the national rate in 2001 was 5.7% (Independent Monitoring Group of the National Cervical Screening Programme, 2004). Similarly, it is possible that some women received cytological tests overseas prior to their diagnosis of cervical cancer within New Zealand, but the numbers are likely to be small.

The available data did not allow for the assessment of whether the smears taken within six months prior to diagnosis were due to the women being symptomatic (*i.e.* diagnostic tests) or were the women's first cytological tests taken at the appropriate time (*i.e.* screening tests). Further investigation, for example, with a case-notes review, would allow for these different scenarios to be distinguished.

A further limitation of the study was that 26% of cases were missing a FIGO code. However, this is unlikely to have biased the findings, particularly the comparisons between Māori and 'Other' women because the proportions missing FIGO codes were very similar (24 and 26%, respectively), and the lowest proportion with missing FIGO stage was actually in Māori women.

We used an area-based measure of SEP (Crampton *et al*, 2004), and it is possible that some individual cases were therefore misclassified. However, the measure used is standard and has shown strong SEP differences for many other health problems (Haynes *et al*, 2008; McFadden *et al*, 2004; Metcalf *et al*, 2008; Robson and Harris, 2007; Tobias and Yeh, 2007); furthermore, information on other possible measures of SEP (*e.g.* income, education, occupation) were not available.

Cervical screening guidelines are extremely complex (National Screening Unit, 2008) and the current study did not assess whether each individual woman had been screened according to the NCSP guidelines – rather, we classified each case according to her screening history (*e.g.* 'regular screening'), irrespective of whether this screening history was consistent with NCSP guidelines. In particular, the cases included some women who would have been too old or too young to have received recent or any screening (if following NCSP guidelines) prior to their diagnosis. Furthermore, it is possible that women have been categorised as 'regular screening' when actually they should have received smears more frequently than once every three years (*e.g.* if they had had a high grade abnormality) if they had been following NCSP guidelines. In contrast, some women may have been regularly screened but may have had 37 or 38 months (rather than 36 months) between two smears and were therefore not categorised as 'regular screening' in the analyses. However, any such discrepancies would have led to a reduction in the protective effect of regular screening found in this study. Conversely, the methodology did not distinguish whether a woman had been rescreened in an interval that was shorter than the standard recommended three years. Women

being screened more frequently in this manner would potentially increase the protective effect of regular screening.

Bearing these strengths and limitations of the data in mind, there are three main findings of this study. First, more than half of the women diagnosed with cervical cancer in New Zealand during 1994-2005 had not been screened more than six months before diagnosis. Secondly, women who were regularly screened had a considerably lower risk of being diagnosed at a late stage. Thirdly, screening history did not appear to explain the ethnic differences in stage at diagnosis.

The first major finding of the study is that the screening rates were relatively low in the cervical cancer cases (Table 3.1) compared with the rates in the general population for 2001 (no national data are available prior to this) to 2006 (Brewer *et al*, 2007b; Brewer *et al*, 2008a; Brewer *et al*, 2008b; Coppell, 2006a; Coppell, 2006b; Independent Monitoring Group of the National Cervical Screening Programme, 2004). More than half (56.7%) of the women had not had a screening smear. This study did not include matched controls without cervical cancer, but information for the general population is available from monitoring reports for the NCSP (Brewer *et al*, 2007b; Brewer *et al*, 2008a; Brewer *et al*, 2008b; Coppell, 2006a; Coppell, 2006b; Independent Monitoring Group of the National Cervical Screening Programme, 2004). Overall, 43.3% of cervical cancer cases had been screened ('ever screened'), compared with ~93% in the general population in 2001 (Independent Monitoring Group of the National Cervical Screening Programme, 2004). Of the cervical cancer cases that had been 'ever screened', 19.7% had 'irregular screening – participation' compared with ~87% in the general population in 2001 (Independent Monitoring Group of the National Cervical

Screening Programme, 2004), 42.4% had 'irregular screening – coverage' compared with 72.7% in the general population in 2001 (Independent Monitoring Group of the National Cervical Screening Programme, 2004), and 32.2% had 'regular screening' (the NCSP monitoring reports do not include 'regular' screening, to the authors' knowledge there is no published information about this in the general population).

These findings are consistent with those of previous studies in other countries which have shown that unscreened women have a higher rate of invasive cervical cancer, and conversely that women with cervical cancer have been screened less often than (hospital) control women or those in the general population (Andrae *et al*, 2008; Bos *et al*, 2006; Stuart *et al*, 1997; Sung *et al*, 2000). No record of screening prior to diagnosis was found for 56.7% of the cases included in the current study, a finding which is similar to the estimates of 53-68% reported in other recent studies (Bos *et al*, 2006; Spayne *et al*, 2007; Sung *et al*, 2000). Screening was particularly low in women with squamous cell carcinoma (41.3%) or adenosquamous cell carcinoma (36.8%), compared with cases of adenocarcinoma (59.7%), a finding which is consistent with previous evidence that screening is less effective for precursors of adenocarcinomas (Boddington *et al*, 1976; Boon *et al*, 1987; Krane *et al*, 2001).

The second major finding of the study is that screening history was associated with stage at diagnosis (Table 3.2). Women that were regularly screened (compared with women that had no screening smears) had a reduced risk of a late stage diagnosis (compared with early stage diagnosis) (OR 0.16, 95% confidence interval 0.10-0.26). Women that met even the weak criterion of 'irregular screening – participation' had a reduced risk (0.17, 0.10-0.31). The apparent 'protective effect' of 'diagnostic only'

screens is difficult to interpret, since the 'diagnostic only' cases probably comprise two distinct groups – those who had genuinely only had a diagnostic smear and those who had had a screening smear. This may explain why the finding for 'diagnostic only' screens (0.39) lies between that for 'regular screening' (0.16) and 'no screening' (the reference category with an OR of 1.0).

As previously stated, there is evidence that screening for precursors for adenocarcinomas is less effective than screening for squamous cell carcinomas (Boddington *et al*, 1976; Boon *et al*, 1987; Krane *et al*, 2001). It is therefore interesting that in the current study the effect (on the OR) of 'regular screening' was stronger in the cases of squamous cell carcinoma (0.12, 0.07-0.23) than in the cases of adenocarcinoma (0.32, 0.13-0.82), but the effect was still strong in the latter group. This is consistent with the finding of Sasieni and Adams that cervical screening seems to have had a substantial impact on the rate of adenocarcinoma in younger women (Sasieni and Adams, 2001).

The third major set of findings involves the ethnic differences in screening history (Table 3.1) and stage at diagnosis (Table 3.3). Rates of 'participation' (a cytology or histology result recorded on the NCSP-R in the previous six years) in the NCSP are substantially lower for Māori and Pacific women (*e.g.* in 2006, 62.4 and 60.4%, respectively) than for non-Māori/non-Pacific women (91.4%) and this is reflected in the lower percentage of screened women of these ethnicities in the current study (Brewer *et al*, 2008b). The percentages 'ever screened' were 24.8% in Pacific women, 30.5% in Asian, 40.6% in Māori, and 46.1% in 'Other' women. The corresponding estimates for 'regular screening' were 5.7, 7.8, 12.5 and 15.3% (Table 3.1).

The current study found that 21.4% of Māori cases had not had a smear prior to their cancer diagnosis, compared with 54% in the study by Ratima *et al* (Ratima *et al*, 1993) which included cases that had occurred before (and in the first two years after) the NCSP was established. However, the current study found that an additional 38% of Māori women had had a smear only in the six months prior to diagnosis, thus suggesting that 59.4% of Māori women had not been 'ever screened'.

Despite the ethnic differences in screening history, adjustment for screening history did not entirely account for the ethnic differences in stage at diagnosis (Table 3.3). For example, the OR for a late stage diagnosis in Māori women (compared with 'Other' women) decreased only from 2.72 (1.99-3.72) to 2.45 (1.77-3.39) when adjusted for screening history. In contrast, the increased risk of late stage diagnosis in Pacific women (compared with 'Other' women; OR 1.45, 0.81-2.61) disappeared when adjusted for screening history (0.99, 0.54-1.81). These data therefore indicate that there is a large excess risk of late-stage diagnosis in Māori women that is not explained by differences in screening history, whereas there is a small excess risk of late-stage diagnosis in Pacific women, which is explained by differences in screening history.

The study was not able to examine the importance of other aetiological factors for cervical cancer survival. Since screening history did not completely explain the ethnic differences in stage at diagnosis, it is important that other possible explanations for these differences should be explored in further studies. These may include delayed diagnosis, *i.e.* some women with regular screening histories may have a longer period of time between a smear that is suggestive of cancer (or the onset of symptoms) and actual

diagnosis of cancer. The reasons for delayed diagnosis and non-participation in screening are complex, but may include barriers to accessing health care (such as language, culture, income and/or education level, and patient-doctor relationship) (Downs *et al*, 2008). There is also some evidence that in New Zealand racial discrimination is associated with poorer self-rated health (Harris *et al*, 2006a; Harris *et al*, 2006b), but there appears to be no evidence directly related to the cervical cancer care pathway in New Zealand. There is some evidence (Brewer *et al*, 2007b; Brewer *et al*, 2008a; Brewer *et al*, 2008b; Coppell, 2006a; Coppell, 2006b; Independent Monitoring Group of the National Cervical Screening Programme, 2004) that histological test results for Māori and Pacific women are reported after a longer period of time than those for non-Māori/non-Pacific women, although it is unclear whether this time difference would actually lead to a late stage at diagnosis since the precursor lesions are known to exist for several years. Failure to be invited or to return for a repeat smear after an unsatisfactory result, or to have a histological specimen taken after a high-grade smear, or a delay in seeing a gynaecologist, as well as not reporting symptoms, may also lead to a delay, resulting in a late stage at diagnosis (Brewer *et al*, 2007b; Brewer *et al*, 2008a; Brewer *et al*, 2008b; Coppell, 2006a; Coppell, 2006b; Independent Monitoring Group of the National Cervical Screening Programme, 2004; Ratima *et al*, 1993).

Conclusions

In conclusion, more than half of the women diagnosed with cervical cancer in New Zealand during 1994-2005 had not been screened more than six months before diagnosis. Women that were regularly screened had a considerably lower risk of being

diagnosed at a late stage, and screening history did not appear to explain the ethnic differences in stage at diagnosis (the increased risk of late-stage diagnosis in Pacific women, compared with 'Other' women, disappeared when adjusted for screening, while that in Māori women remained largely unexplained). These findings indicate that, in order to reduce further the proportion of women who are diagnosed with cervical cancer at a late stage, major efforts should continue to increase the proportion of women who participate in the NCSP and to encourage women to participate in the screening programme on a regular basis. Further investigation is required to elucidate the reasons for the increased risk of a late stage diagnosis in Māori women that persists after adjustment for screening history, SEP and urban/rural residency.

CHAPTER 4

Does comorbidity explain the ethnic inequalities in cervical cancer survival in New Zealand? A retrospective cohort study

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Background: There are large ethnic differences in cervical cancer survival in New Zealand that are only partly explained by stage at diagnosis. We investigated the association of comorbidity with cervical cancer survival, and whether comorbidity accounted for the previously observed ethnic differences in survival.

Methods: The study involved 1,594 cervical cancer cases registered during 1994-2005. Comorbidity was measured using hospital events data and was classified using the Elixhauser instrument; effects on survival of individual comorbid conditions from the Elixhauser instrument were also assessed. Cox regression was used to estimate adjusted cervical cancer mortality hazard ratios (HRs).

Results: Comorbidity during the year before diagnosis was associated with cervical cancer-specific survival: those with an Elixhauser count of ≥3 (compared with a count of zero) had a HR of 2.17 (1.32-3.56). The HR per unit of Elixhauser count was 1.25 (1.11-1.40). However, adjustment for the Elixhauser instrument made no difference to the mortality HRs for Māori and Asian women (compared with 'Other' women), and made only a trivial difference to that for Pacific women. In contrast, concurrent adjustment for 12 individual comorbid conditions from the Elixhauser instrument reduced the Māori HR from 1.56 (1.19-2.05) to 1.44 (1.09-1.89), *i.e.* a reduction in the excess risk of 21%; and reduced the Pacific HR from 1.95 (1.21-3.13) to 1.62 (0.98-2.68), *i.e.* a reduction in the excess risk of 35%.

Conclusions: Comorbidity is associated with cervical cancer-specific survival in New Zealand, but accounts for only a moderate proportion of the ethnic differences in survival.

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Background

In 2005, cervical cancer was the ninth most common site of cancer registration for New Zealand females (Ministry of Health, 2009a), and the incidence and mortality rates were moderately high compared with the rest of the developed world (The Descriptive Epidemiology Group of IARC, 2002). Incidence and mortality rates are not the same across ethnic groups within New Zealand. For example, in 2005, Māori women had an incidence rate of 9.0, Pacific women 16.3 and 'Other' (predominantly European) women 5.6 per 100,000 women; Māori women had a mortality rate of 6.5, Pacific women 7.1 and 'Other' women 1.4 per 100,000 women (Ministry of Health, 2009a).

We have previously reported demographic differences in cervical cancer survival in New Zealand (Brewer *et al*, 2009). Māori and Pacific women had higher death rates than 'Other' women, whereas Asian women had a lower risk. Adjustment for stage at diagnosis, socio-economic position (SEP), and urban/rural residency explained only some of the increased risks in Māori and Pacific women. Ethnic differences in stage at diagnosis were not entirely explained by differences in screening history (Brewer *et al*, 2010; Priest *et al*, 2010). There is some evidence of limited differences in treatment between Māori and non-Māori women, but these differences have little impact on survival differences (McLeod *et al*, 2010). Thus, the reasons for the differences in survival are currently unclear, but one possibility not previously examined is that they may, in part, be due to differences in comorbidity at the time of cervical cancer diagnosis. Māori and Pacific women have higher rates of many diseases, including smoking-related respiratory diseases, diabetes and cardiovascular disease (Ministry of Health, 2008b; Ministry of Health and Ministry of Pacific Island Affairs, 2004; Robson

and Harris, 2007). Such comorbid conditions may have effects prior to diagnosis (*e.g.* influence the likelihood of cancer screening or late stage diagnosis) (Fleming *et al*, 2005; Fleming *et al*, 2006), or affect survival post-diagnosis either directly (*e.g.* some comorbid conditions may adversely affect prognosis) or indirectly (*e.g.* some comorbid conditions may affect or limit treatment options or decisions). In New Zealand, comorbidity has been found to contribute to ethnic-specific survival disparities for colon cancer (Hill *et al*, 2010), the management of stages I and II non-small-cell lung cancer (Stevens *et al*, 2008c), and adverse event status, inpatient death and increased length of stay in selected Auckland hospitals (Davis *et al*, 2002). Internationally, comorbidity has also been found to adversely affect survival in patients with a range of conditions, including cervical cancer (Coker *et al*, 2009b; D'Hoore *et al*, 1993; Hopkins and Morley, 1991; Peipert *et al*, 1994; Piccirillo *et al*, 2004; Tammemagi *et al*, 2003; van der Aa *et al*, 2008).

We therefore investigated the associations of various comorbid conditions with cervical cancer survival, and whether these comorbid conditions accounted for the previously observed ethnic differences in survival.

Methods

The source population comprised all cervical cancer cases registered with the New Zealand Cancer Registry (NZCR) between 1 January 1994 and 31 December 2005 (Brewer *et al*, 2010; Brewer *et al*, 2009). The NZCR records self-identified ethnicity, and allows for multiple responses. Participants who reported more than one ethnicity were classified into a single ethnicity using the standard system of prioritisation:

Māori>Pacific>Asian>'Other' (New Zealand Department of Statistics, 1990). Participants with missing ethnicity data were included in the 'Other' (predominantly European) ethnic group in the analyses. This approach is standard practice in New Zealand health research (Ministry of Health, 2002; Ministry of Health, 2006). All registrations include the National Health Index (NHI) number which uniquely identifies individual health care users; this was used to obtain cause-specific mortality data (from the Mortality Collection) up to the end of December 2005 (the most recent year for which data was available), and hospital events data (from the National Minimum Dataset (NMDS); up to 99 diagnosis/procedure codes may be provided to the NMDS) from 1988 to 31 December 2005.

SEP was estimated using the New Zealand Deprivation Index 2001 (NZDep2001), an area-based measure derived from a combination of nine socioeconomic variables derived from the national census (Crampton *et al*, 2004). Each participant was assigned a score based upon the residential area (the domicile code) in which they lived, as recorded on the NZCR at the time of registration. These scores were then grouped into quintiles (Crampton *et al*, 2004).

The domicile code recorded for each participant was also used to assign urban/rural residency according to population size (Statistics New Zealand, 2008). Participants were classified as living in a main urban area (with a population of ≥30,000), a secondary or minor urban area (population ≥1,000 to 29,999), or a rural area (population <1,000).

Data on stage at diagnosis were obtained from the NZCR, and reported using the International Federation of Gynecology and Obstetrics (FIGO) system (Benedet *et al*, 2006). In order to provide sufficient numbers in each category, the FIGO stages were grouped into four categories: stages 0-IB2; II-IIB; III-IIIB; IVA-IVB. A fifth category of 'missing' was utilised for cases where the FIGO stage was unknown. We conducted a basic sensitivity analysis, to assess the potential for bias resulting from the exclusion of the women with missing stage data; this involved three sets of analyses: (i) adjusting for stage and excluding the women with missing stage data; (ii) including the women with and without missing stage data, and adjusting for stage with a dummy variable representing the women with missing stage data; and (iii) including the women with and without missing stage data, but not adjusting for stage. The three sets of analyses yielded the same patterns. We therefore present here the findings from the first method (*i.e.* excluding women with missing stage), because it is necessary to adjust for stage, and this is the only approach that enables us to do this validly (Brewer *et al*, 2010; Brewer *et al*, 2009).

We used two widely utilised comorbidity measures. The Elixhauser instrument (Elixhauser *et al*, 1998) was designed specifically for use with administrative data, and is based on a set of 30 comorbid conditions which were associated with increased length of stay, hospital charges and mortality among non-maternal inpatients in California in 1992 (Elixhauser *et al*, 1998). The Charlson Comorbidity Index (CCI) (Charlson *et al*, 1987) comprises 19 comorbid conditions which are given a weight of 1 to 6 on the basis of the strength of their association with one-year mortality among a cohort of 607 general medical patients in the United States (Charlson *et al*, 1987). To our knowledge this is the first study of the role of comorbidity in cervical cancer survival in New

Zealand, and there were therefore no prior data on which of these two (or any other) comorbidity measures were most appropriate to use. In general, we found very similar results with the two comorbidity measures, and we have therefore reported only the findings for the Elixhauser instrument (the findings for the CCI are available in Appendix 1, Tables A1.1-A1.4); effects on survival of individual comorbid conditions from the Elixhauser instrument were also assessed.

Comorbidity was assessed, using the hospital events data, according to the enhanced ICD-9-CM (for data from 1988-1999) and ICD-10 (for data from 2000-2005) coding algorithms of Quan *et al* (Quan *et al*, 2005) for the Elixhauser instrument (Elixhauser *et al*, 1998) and the CCI (Charlson *et al*, 1987). We used both the primary and the secondary diagnoses fields to identify comorbid conditions during the period one year, and the period five years, preceding, and including, the date of diagnosis. The optimal look-back period (the time over which to identify comorbid conditions) was not clear since shorter times may capture more active conditions and longer periods may be more likely to identify all of the important comorbid conditions (Preen *et al*, 2006). We therefore utilised two look-back periods, with five years being the longest timeframe over which we had data for all of the women. In general, we found similar results with the two look-back periods (see Appendix 1, Tables A1.1-A1.3), though the associations of comorbidity with survival were somewhat stronger when using the one-year look-back period; we therefore only report here the findings for the one-year look-back period. We included comorbid conditions identified up to and including the date of diagnosis to strike a balance between identifying all of the comorbid conditions that the women had at the time of diagnosis whilst attempting to avoid including conditions that may have been caused by treatment after diagnosis. Metastatic solid tumours were

excluded from both comorbidity algorithms, as were all diagnosis codes for cervical cancer. For each woman, the comorbidity frequency (for the Elixhauser instrument) and score (for the CCI) were recorded (for use as continuous variables) and were also then categorised into (two sets of) four groups (0, 1, 2, and ≥3).

The Elixhauser measure was calculated using the Statistical Analysis System (SAS) software 9.1, whilst all other analyses were conducted using Intercooled Stata 10 for Windows (StataCorp, College Station, Texas, USA). The Cox proportional hazards model (Cox, 1972) was used to estimate the hazard ratios (HRs) for cervical cancer mortality, 'other mortality' (non-cervical cancer), and total mortality associated with the Elixhauser count, as well as with ethnicity, NZDep2001, and urban/rural residency, adjusted for age, registration year, and stage at diagnosis. Women were censored at the time of their death or on 31 December 2005 if they were still alive at that time (Brewer *et al*, 2009). In the final set of analyses, the HRs for each ethnic group were estimated adjusted for the Elixhauser count, and, finally, for the individual comorbid conditions that had a HR of ≥1.5.

The New Zealand Central Ethics Committee granted ethical approval for the study (CEN/08/04/EXP).

Results

There were 2,323 cases of cervical cancer registered on the NZCR between 1 January 1994 and 31 December 2005, and all of these cases were included in the descriptive analyses of comorbidity (Table 4.1). Using a one-year look-back period, 15.6% of cases

had had at least one comorbidity (included in the Elixhauser instrument) event in the year before diagnosis; the percentages were similar in Asian (13.3%) and 'Other' women (13.7%), but were highest in Pacific women (32.4%), with Māori women having an intermediate value (19.7%). The Elixhauser count was strongly associated with NZDep2001, and FIGO stage, but was only weakly associated with urban/rural residency and time period of diagnosis.

For the analyses of the effects of comorbidity on mortality (Table 4.2), the following exclusions were made; 621 because they did not have a FIGO code (including 17 women whose cancer registration was made on the date of the their death, and 50 women that could not be assigned an NZDep2001 score), 77 cases because they did not have a domicile code that could be assigned an NZDep2001 score, and a further 31 cases because they were diagnosed after 30 June 2005 (and therefore had a potential follow-up time of less than six months), leaving 1,594 women to be included in the analyses. The women that were excluded because they did not have a FIGO code had a similar ethnic and SEP distribution to the cases that did have a FIGO code (Brewer *et al*, 2010).

Of the 1,594 women included in the analyses: 99.2% were diagnosed based upon the histology of the primary malignant tumour (Brewer *et al*, 2009); 1,163 (73%) identified as 'Other' ethnicity, 312 of whom died during the follow-up period, 241 (77%) due to cervical cancer, and 71 (23%) due to other causes; 292 identified as Māori ethnicity (18%), 104 of whom died, 92 (88%) due to cervical cancer, and 12 (12%) due to other causes; 59 (4%) identified as Pacific ethnicity, 20 of whom died, 20 (100%) due to cervical cancer; and, 80 (5%) identified as Asian ethnicity, 14 of whom died, 13 (93%) due to cervical cancer, and 1 (7%) due to other causes.

Table 4.1. Characteristics of cervical cancer cases, n (%)

	Total	*Elixhauser comorbid conditions*			
		0	*1*	*2*	*3+*
Total	2,323 (100)	1,960 (84.4)	223 (9.6)	63 (2.7)	77 (3.3)
FIGO stage					
0-IB2	1,155 (49.7)	1,067 (92.4)	63 (5.5)	13 (1.1)	12 (1.0)[a]
II-IIB	262 (11.3)	207 (79.0)	32 (12.2)	11 (4.2)	12 (4.6)
III-IIIB	232 (10.0)	169 (72.8)	41 (17.7)	16 (6.9)	6 (2.6)
IVA-IVB	53 (2.3)	33 (62.3)	11 (20.8)	3 (5.7)	6 (11.3)
Missing	621 (26.7)	484 (77.9)	76 (12.2)	20 (3.2)	41 (6.6)
Ethnicity					
Other	1,674 (72.1)	1,444 (86.3)	141 (8.4)	41 (2.5)	48 (2.9)[a]
Māori	416 (17.9)	334 (80.3)	50 (12.0)	15 (3.6)	17 (4.1)
Pacific	105 (4.5)	71 (67.6)	21 (20.0)	3 (2.9)	10 (9.5)
Asian	128 (5.5)	111 (86.7)	11 (8.6)	4 (3.1)	2 (1.6)
NZDep2001, quintiles					
1 (Least deprived)	298 (12.8)	277 (93.0)	14 (4.7)	3 (1.0)	4 (1.3)[b]
2	333 (14.3)	283 (85.0)	33 (9.9)	8 (2.4)	9 (2.7)
3	416 (17.9)	350 (84.1)	37 (8.9)	12 (2.9)	17 (4.1)
4	526 (22.6)	432 (82.1)	56 (10.7)	19 (3.6)	19 (3.6)
5 (Most deprived)	623 (26.8)	510 (81.9)	67 (10.8)	21 (3.4)	25 (4.0)
Missing	127 (5.5)	108 (85.0)	16 (12.6)	0	3 (2.4)
Urban/rural residency					
Main urban	1,640 (70.6)	1,403 (85.6)	141 (8.6)	42 (2.6)	54 (3.3)[NS]
Secondary urban	361 (15.5)	288 (79.8)	47 (13.0)	13 (3.6)	13 (3.6)
Rural	196 (8.4)	162 (82.7)	19 (9.7)	8 (4.1)	7 (3.6)
Missing	126 (5.4)	107 (84.9)	16 (12.7)	0	3 (2.4)
Registration year					
1994-1997	843 (36.3)	714 (84.7)	82 (9.7)	24 (2.9)	23 (2.7)[NS]
1998-2001	815 (35.1)	689 (84.5)	79 (9.7)	20 (2.5)	27 (3.3)
2002-2005	665 (28.6)	557 (83.8)	62 (9.3)	19 (2.9)	27 (4.1)

FIGO: International Federation of Gynecology and Obstetrics; NZDep2001: New Zealand Deprivation Index 2001; NS: Not significant at 5%. p value based on Pearson's chi-squared. [a]p=0.0001; [b]p=0.02.

Table 4.2. Mortality by comorbidity

Comorbidity	*HR (95%CI)*[a]
Death from cervical cancer	
Elixhauser (1 unit)	1.25 (1.11-1.40)
Elixhauser 0	1.00[b]
Elixhauser 1	1.29 (0.96-1.75)
Elixhauser 2	1.33 (0.83-2.13)
Elixhauser 3+	2.17 (1.32-3.56)
Death from other causes (not cervical cancer)	
Elixhauser (1 unit)	1.46 (1.18-1.79)
Elixhauser 0	1.00[b]
Elixhauser 1	2.49 (1.39-4.44)
Elixhauser 2	2.62 (1.20-5.72)
Elixhauser 3+	2.76 (1.04-7.30)
Total mortality	
Elixhauser (1 unit)	1.28 (1.15-1.41)
Elixhauser 0	1.00[b]
Elixhauser 1	1.47 (1.13-1.92)
Elixhauser 2	1.48 (0.99-2.21)
Elixhauser 3+	2.20 (1.41-3.41)

HR (95%CI): Hazard ratio (95% confidence intervals). [a]Adjusted for age, registration year, stage, ethnicity, socioeconomic position, and urban/rural residency. [b]Reference category.

Table 4.2 shows the HRs for cervical cancer survival by comorbidity, adjusted for age, registration year, stage, ethnicity, NZDep2001, and urban/rural residency. Comorbid disease in the year before diagnosis was associated with cervical cancer-specific survival: those with an Elixhauser count of 3 or more had a HR of 2.17 (95% confidence intervals 1.32-3.56). The HR was associated with a per-unit increase (when analysing the Elixhauser instrument as a continuous variable) of 1.25 (1.11-1.40). Comorbidity was more strongly associated with mortality from conditions other than cervical cancer: those with an Elixhauser count of 3 or more had a HR for other mortality of 2.76 (1.04-7.30). The HR was associated with a per unit increase of 1.46 (1.18-1.79).

We estimated the cervical cancer-specific survival HRs adjusted for age, registration year, stage, ethnicity, NZDep2001 and urban/rural residency, for those with individual conditions included in the Elixhauser instrument (see Appendix 1, Table A1.3). Thirteen of the individual comorbid conditions showed HRs of ≥1.5 in the one-year look-back period; congestive heart failure (2.35, 95% confidence intervals 1.22-4.52), valvular disease (2.84, 0.70-11.61), complicated hypertension (1.74, 0.24-12.72), chronic pulmonary disease (1.62, 0.95-2.77), uncomplicated diabetes (2.17, 1.33-3.53), complicated diabetes (10.46, 3.01-36.37), renal failure (4.27, 2.08-8.76), liver disease (2.43, 0.76-7.78), coagulopathy (2.78, 0.68-11.43), obesity (3.52, 1.55-7.98), fluid and electrolyte disorders (4.03, 2.01-8.08), blood loss anaemia (2.44, 1.48-4.00), and drug abuse (3.28, 0.45-23.76). We therefore adjusted for these individual comorbid conditions in the final analyses, except for uncomplicated diabetes because the methodology of the Elixhauser instrument allows for a woman to be recorded as having both uncomplicated and complicated diabetes (where the Elixhauser count was used,

only complicated diabetes (or complicated hypertension) was included when the woman also had uncomplicated diabetes (or uncomplicated hypertension)).

Table 4.3 shows the findings for ethnic differences in cervical cancer-specific survival adjusted for comorbidity as a continuous variable and for the 12 individual comorbid conditions. Adjustment for the Elixhauser count made no difference to the cervical cancer-specific survival HRs for Māori and Asian women (compared to 'Other' women), and made only a trivial difference to that for Pacific women. The largest change was for Pacific women, where the HR fell from 1.95 (1.21-3.13) to 1.92 (1.20-3.09). However, the HRs changed more substantially when adjustment was made for all 12 of the individual comorbid conditions; the HR for Māori women fell from 1.56 (1.19-2.05) to 1.44 (1.09-1.89), representing a 21% decrease in the excess mortality risk; the HR for Pacific women fell from 1.95 (1.21-3.13) to 1.62 (0.98-2.68), representing a 35% decrease in the excess mortality risk.

Table 4.3. Cervical cancer-specific mortality by ethnicity adjusted for comorbidity

Comorbidities	*Comorbidity*	*Ethnicity*			
		Other	*Māori*	*Pacific*	*Asian*
	HR (95%CI)[a]	*HR (95%CI)[b]*	*HR (95%CI)[c]*	*HR (95%CI)[c]*	*HR (95%CI)[c]*
No comorbidity adjustment/inclusion		1.00	1.56 (1.19-2.05)	1.95 (1.21-3.13)	0.72 (0.41-1.27)
Elixhauser as continuous variable	1.25 (1.11-1.40)	1.00	1.55 (1.19-2.04)	1.92 (1.20-3.09)	0.72 (0.41-1.26)
Individual comorbities					
Congestive heart failure	2.35 (1.22-4.52)	1.00	1.57 (1.20-2.06)	1.98 (1.23-3.17)	0.72 (0.41-1.27)
Valvular disease	2.84 (0.70-11.61)	1.00	1.56 (1.19-2.04)	1.96 (1.22-3.14)	0.72 (0.41-1.27)
Hypertension, complicated	1.74 (0.24-12.72)	1.00	1.57 (1.19-2.06)	1.95 (1.22-3.13)	0.72 (0.41-1.27)
Chronic pulmonary disease	1.62 (0.95-2.77)	1.00	1.55 (1.18-2.03)	1.95 (1.22-3.13)	0.67 (0.38-1.19)
Diabetes, complicated	10.46 (3.01-36.37)	1.00	1.55 (1.18-2.04)	1.70 (1.03-2.80)	0.71 (0.40-1.25)
Renal failure	4.27 (2.08-8.76)	1.00	1.58 (1.20-2.07)	1.70 (1.04-2.77)	0.72 (0.41-1.27)
Liver disease	2.43 (0.76-7.78)	1.00	1.55 (1.18-2.03)	1.92 (1.20-3.09)	0.72 (0.41-1.26)
Coagulopathy	2.78 (0.68-11.43)	1.00	1.55 (1.18-2.03)	1.91 (1.19-3.07)	0.72 (0.41-1.27)
Obesity	3.52 (1.55-7.98)	1.00	1.55 (1.18-2.04)	1.90 (1.18-3.05)	0.72 (0.41-1.27)
Fluid and electrolyte disorders	4.03 (2.01-8.08)	1.00	1.51 (1.15-1.98)	1.97 (1.23-3.16)	0.69 (0.39-1.21)
Blood loss anaemia	2.44 (1.48-4.00)	1.00	1.53 (1.17-2.01)	1.98 (1.23-3.17)	0.71 (0.40-1.26)
Drug abuse	3.28 (0.45-23.76)	1.00	1.56 (1.19-2.04)	1.95 (1.22-3.13)	0.72 (0.41-1.27)
Multivariate - all 12 of the above		1.00	1.44 (1.09-1.89)	1.62 (0.98-2.68)	0.63 (0.35-1.13)

HR (95%CI): Hazard ratio (95% confidence intervals). [a]Adjusted for age, registration year, stage, ethnicity, socioeconomic position, and urban/rural residency. [b]Reference category. [c]Adjusted for age, registration year, stage, ethnicity, socioeconomic position, urban/rural residency, and comorbidity index.

Discussion

This study found that comorbidity is associated with cervical cancer-specific mortality and more strongly with mortality from other causes. This latter finding is not surprising since some cervical cancer patients who have a comorbidity may die from this comorbidity, and this group would therefore be expected to have a higher death rate from 'other causes' (*i.e.* all causes of death other than cervical cancer) than cervical cancer patients who do not have a comorbidity.

Adjusting for the Elixhauser instrument produced little change in the ethnic differences in mortality. In contrast, adjustment for 12 individual comorbid conditions included in the Elixhauser instrument reduced the excess HR for Māori women by 21% and for Pacific women by 35%.

A strength of the study is that the Cancer Registry Act came into effect in 1994 making cancer registration mandatory (Ministry of Health, 2009a), and case under-ascertainment unlikely (Ministry of Health, 2002). Death registration is also mandatory in New Zealand, and can be linked to cancer registrations using the NHI number; thus there is a high probability that the study identified all of the cases that died in New Zealand. There may have been some misclassification of cause of death, but it is unlikely to have produced significant bias in the ethnic comparisons (Sarfati *et al*, 2010a). Furthermore, classification of the cause of death for patients on the NZCR is highly accurate since in cases that are registered prior to death, information from the NZCR is used to classify the underlying cause of death (New Zealand Health Information Service, 2004).

Other possible limitations of the study include the potential misclassification of ethnicity, which has been estimated to produce a 17% undercount of Māori cancer registrations (Cormack *et al*, 2005) (this involves misclassification of ethnicity on registrations, rather than case under-ascertainment). Thus, the 'Other' ethnic group may contain some Māori cases that were incorrectly classified, thereby diluting the ethnic survival differences. There is also evidence of a 6–7% undercount of Māori deaths (Ajwani *et al*, 2003a; Cormack *et al*, 2005), but this would not bias the current study since the ethnicity recorded on the NZCR was used in all analyses. The classification of ethnicity was based on the wording of the corresponding census questions, and these have changed over time, but once again this is unlikely to have produced serious bias because the ethnicity recorded on the NZCR was also used to classify the corresponding deaths, and the analyses were adjusted for registration year. There may also be misclassification of area-based SEP and urban/rural residency in cancer registrations, but in each instance, any such misclassification is unlikely to be associated with subsequent survival and, if anything, is likely to produce underestimates of the differences in survival between these various demographic groups.

The greatest change in the ethnic-specific HRs occurred when adjustment was made for the 12 individual comorbid conditions, rather than using the summary Elixhauser comorbidity measure. Some of these individual comorbid conditions may have shown elevated HRs by chance, because of the large number of comparisons involved.

The comorbidity data were based on administrative in-hospital data and therefore some conditions may not have been recorded. However, a study on colon cancer in New

Zealand found that, despite comorbid conditions being recorded more frequently in patients' medical notes than in administrative data, the use of a comorbidity measure still improved the prediction of all-cause survival in a multivariable model (Sarfati *et al*, 2010b). It is also possible that some patients had undiagnosed disease, which may have been more common in Māori and Pacific women, but misclassification of this type would probably decrease the effect of comorbidity on survival (Sarfati *et al*, 2010b).

To date, there have been few studies of the role of comorbid conditions in cervical cancer survival, and none in New Zealand. Our results are generally consistent with those of Coker *et al* (Coker *et al*, 2009b) who found that in Texan women aged 65 years or older with cervical cancer, those that had one or more comorbid conditions were 40% more likely to die (from all causes) compared with women who did not have any comorbid conditions. However, unlike Coker *et al* (Coker *et al*, 2009b) who did not find an independent association between comorbidity and cervical cancer-specific survival, we found an independent 25% increased risk of death from cervical cancer for each unit increase of the Elixhauser count (Table 4.3). In a study of stage IB squamous cell carcinoma, Hopkins and Morley (Hopkins and Morley, 1991) found that women with diabetes had an 82% cumulative 5-year all-cause survival compared with an 89% survival in those who did not have diabetes (p=0.04). These findings are also consistent with the 10-fold increased risk of cervical cancer-specific mortality in the present study. In contrast to our study, Leath *et al* (Leath *et al*, 2005) did not find comorbid conditions to be an independent predictor of survival in women with either early or late stage cervical cancer.

The present study has shown that Māori and Pacific women have a larger number of comorbid conditions than 'Other' and Asian women when measured with the Elixhauser instrument with a one-year look-back period (Table 4.1). Women living in more deprived areas had larger numbers of comorbid conditions according to the Elixhauser instrument. We found independent associations between the Elixhauser count and cervical cancer-specific, 'other' and total mortality (Table 4.2).

Reducing ethnic inequalities in cancer is one of the overall purposes of the New Zealand Cancer Control Strategy (Minister of Health, 2003). We and others (Brewer *et al*, 2009; Ministry of Health, 2009a; National Cervical Screening Programme, 2005; Robson *et al*, 2006) have previously demonstrated substantial ethnic inequalities in cervical cancer incidence, mortality and survival in New Zealand. It has been suggested (Jeffreys *et al*, 2005b) that comorbid conditions, which are known to differ between ethnic groups (Ministry of Health, 2008b), could account for these inequalities and, as mentioned earlier, there is some international evidence of comorbidity adversely affecting cervical cancer survival (Coker *et al*, 2009b; Hopkins and Morley, 1991; Peipert *et al*, 1994). The current study, the first to empirically investigate this issue in New Zealand, only partially supports this hypothesis. It is possible that there are small ethnic differences at each stage of the cancer continuum (screening, diagnosis, treatment, comorbidity, follow-up, *etc*) and that each of these makes a small contribution to the major overall ethnic differences in survival that we have reported.

Conclusion

In summary, we assessed the roles of comorbid conditions identified through hospital events data and found that these conditions are associated with cervical cancer-specific mortality, but account for only a moderate proportion of the ethnic differences in survival. Other factors, including possible differences in treatment and follow-up, may also play a role.

CHAPTER 5

Travel time and distance to healthcare, and inequalities in cervical cancer screening, stage at diagnosis and mortality in New Zealand

Naomi Brewer, Barry Borman, Peter Day, Neil Pearce

Objective: To investigate whether travel time or travel distance to the nearest General Practitioner (GP) and/or cancer centre accounts for the ethnic differences in cervical cancer screening, stage at diagnosis and mortality in New Zealand.

Methods: The study involved 1,594 cervical cancer cases registered during 1994-2005. Travel time and distance to the GP and cancer centre were estimated using a Geographical Information System. Logistic regression was used to estimate associations between travel time and distance and screening history and stage at diagnosis. Cox regression was used to estimate adjusted cervical cancer mortality hazard ratios.

Results: Adjustment for travel time or distance made almost no difference to ethnic differences in screening rates. Adjustment for travel time reduced the excess risk for late stage diagnosis by 7% in Māori and 33% in Pacific women. Travel time was only weakly and inconsistently associated with cervical cancer mortality (adjusted for stage), and adjustment for travel time reduced the excess risk for mortality by 3% in Māori and 13% in Pacific women. Similar findings were observed when using travel distance rather than travel time.

Conclusions: Travel time and distance are only weakly associated with cervical cancer screening, stage at diagnosis and mortality in New Zealand. However, travel time may account for a small proportion of the ethnic differences in stage at diagnosis, and to a lesser extent mortality, particularly for Pacific women.

Implications: The findings suggest that there may be ethnic variations in access to treatment or treatment quality, which may be related to travel time.

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Introduction

In 2007, cervical cancer was the thirteenth most common site of cancer registration for New Zealand females (Ministry of Health, 2010a), and the incidence and mortality rates were relatively low compared with the rest of the developed world (Ferlay *et al*, 2010). However, incidence and mortality rates are not the same across ethnic groups within New Zealand. For example, in 2005, Māori women had an incidence rate of 9.0, Pacific women 16.3 and 'Other' (predominantly European) women 5.6 per 100,000 women; Māori women had a mortality rate of 6.5, Pacific women 7.1 and 'Other' women 1.4 per 100,000 women (Ministry of Health, 2009a).

There are major demographic differences in cervical cancer screening (Brewer *et al*, 2010), stage at diagnosis (Brewer *et al*, 2009) and mortality in New Zealand (Brewer *et al*, 2009; Priest *et al*, 2010). We have previously reported (Brewer *et al*, 2009) that Māori and Pacific women had higher death rates than 'Other' women, whereas Asian women had a lower risk. Adjustment for stage at diagnosis, socio-economic position (SEP), and urban/rural residency explained only some of the increased risks in Māori and Pacific women. Ethnic differences in stage at diagnosis were not entirely explained by differences in screening history (Brewer *et al*, 2010). Adjustment for comorbid conditions accounted for only a moderate proportion of the ethnic differences in mortality (Brewer *et al*, 2011b).

Thus, the reasons for the ethnic differences in mortality are currently unclear, but one possibility not previously examined is that they may, in part, be due to differences in travel time and/or distance to the nearest General Practitioner (GP) and/or cancer

treatment centre. Travel time and distance could impact on mortality by affecting rates of screening and therefore stage at diagnosis or by impacting mortality more directly by affecting access to, or utilisation of, treatment once women have been diagnosed.

Internationally, several studies have shown travel distance to, or remoteness from, GP practices and cancer treatment facilities, to have a negative impact on cancer mortality and survival (Campbell *et al*, 2000; Jones *et al*, 2008; O'Brien *et al*, 2000; Tan *et al*, 2009). These effects may be mediated through later stage at diagnosis and lower utilisation of health services, possibly because of the higher financial costs and inconvenience (Jones *et al*, 2008). Travel time and distance, and the associated costs and inconvenience of transportation, have been shown to be a perceived barrier to care (Payne *et al*, 2000) and may lead to "patients opting to forgo needed care" (Guidry *et al*, 1997), especially in ethnic minorities.

However, not all studies internationally have found travel distance or remoteness to have a negative association with survival (Koka *et al*, 2002). New Zealand studies have also found inconsistent associations between travel distance or remoteness and cancer stage, mortality and survival (Bennett *et al*, 2007; Brewer *et al*, 2009; Gill and Martin, 2002; Haynes *et al*, 2008). Haynes *et al* (Haynes *et al*, 2008) found no evidence of a later stage at diagnosis in those living furthest from either a cancer centre or a GP. They found poorer survival in prostate cancer patients who had longer travel times to a GP, and for patients with colorectal, breast or prostate cancer who had longer travel times to a cancer centre. However, they did not find the same trends for lung cancer or melanoma patients. Bennett *et al* (Bennett *et al*, 2007) did not find an association between urban/rural residency and breast cancer stage or survival. Gill and Martin (Gill

and Martin, 2002) found an inconsistent association between distance from a major cancer centre and upper gastrointestinal cancer, with those living 51-100 kilometres (km) away having a worse prognosis than those living >200 km away.

There are geographic and ethnic variations in GP accessibility in New Zealand. Generally Māori have longer travel times to their nearest GP; because a relatively high proportion of Māori live in rural areas; Pacific people generally have shorter travel times, because a relatively high proportion live in urban areas (Brabyn and Barnett, 2004). However, there have been few studies of the effects of travel time or distance on cancer survival in New Zealand (Bennett *et al*, 2007; Brewer *et al*, 2009; Gill and Martin, 2002; Haynes *et al*, 2008). A distinctive feature of cervical cancer, unlike most of the cancers that have been studied in New Zealand previously, with the exception of breast cancer, is that there is a national screening programme, and the possibility therefore exists to examine the associations between travel time and/or distance and screening history, stage at diagnosis and cervical cancer mortality. We have therefore investigated the associations of travel time and travel distance with cervical cancer screening, stage at diagnosis and mortality, and whether travel time and/or distance accounted for the previously observed ethnic differences.

Methods

The source population comprised all cervical cancer cases registered with the New Zealand Cancer Registry (NZCR) between 1 January 1994 and 31 December 2005 (Brewer *et al*, 2010; Brewer *et al*, 2009). The NZCR records self-identified ethnicity, and allows for multiple responses. Participants who reported more than one ethnicity

were classified into a single ethnicity using the standard system of prioritisation: Māori>Pacific>Asian>'Other' (New Zealand Department of Statistics, 1990). Participants with missing ethnicity data were included in the 'Other' (predominantly European) ethnic group in the analyses. This approach is standard practice in New Zealand health research (Ministry of Health, 2002; Ministry of Health, 2006). All registrations include the National Health Index (NHI) number which uniquely identifies individual health care users; this was used to obtain cause-specific mortality data (from the Mortality Collection) up to the end of December 2005 (the most recent year for which data was available), and to obtain the woman's cervical screening history from the National Cervical Screening Programme Register.

The classifications of screening history were based on those used for the New Zealand Cervical Cancer audit (Sadler *et al*, 2004) and for quality monitoring by the NCSP (Ministry of Health, 2000). Women were categorized as 'not screened' or 'ever screened'. We excluded all of the smears taken in the six months immediately prior to diagnosis since some of these will have been taken for diagnostic, not screening, purposes (Sasieni *et al*, 2003; Spayne *et al*, 2007). The full details of the categorisation have been described elsewhere (Brewer *et al*, 2010). Cervical screening guidelines are extremely complex (National Screening Unit, 2008), and the categories used in this study are therefore only able to approximate the women's screening histories (Sadler *et al*, 2004).

SEP was estimated using the New Zealand Deprivation Index 2001 (NZDep2001), an area-based measure derived from a combination of nine socioeconomic variables derived from the national census (Crampton *et al*, 2004). Each participant was assigned

a score based upon the residential area (the domicile code) in which they lived, as recorded on the NZCR at the time of registration. These scores were then grouped into quintiles (Crampton *et al*, 2004).

Data on stage at diagnosis were obtained from the NZCR, and reported using the International Federation of Gynecology and Obstetrics (FIGO) (Benedet *et al*, 2006) system. In order to provide sufficient numbers in each category, the FIGO stages were grouped into four categories: stages 0-IB2; II-IIB; III-IIIB; IVA-IVB. The FIGO stages were also further grouped into early stage (FIGO stages 0-IB2) and late stage (FIGO stages II-IVB) for some analyses. Women with an unknown stage at diagnosis, or who could not be allocated a deprivation score, were excluded from the analyses. There was little ethnic or socioeconomic difference in the percentage of cases with missing FIGO codes (Brewer *et al*, 2010).

The methods used to estimate travel time and distance to the nearest GP and cancer centre were based on those of Haynes *et al* (Haynes *et al*, 2008) and Pearce *et al* (Pearce *et al*, 2006). Both travel time and distance were used in order to measure accessibility more accurately. The domicile code recorded for each participant was matched to a 2001 Census Area Unit (CAU), allowing a location to be assigned to each participant. The travel time (in minutes, and fractions of minutes) and distance (in metres) to the nearest GP surgery (n=1383) and to the nearest of the six cancer centres were calculated from the population-weighted centroids of each of the 1,860 CAUs across New Zealand, using the road network functionality in a geographical information system (GIS) (Haynes *et al*, 2008). The travel times and distances were then categorised according to the method of Haynes *et al* (Haynes *et al*, 2008): Low: the lowest quartile

using the whole sample; Medium: quartiles two and three, incorporating half the records around the median; High: records between the 75 and 95 percentiles; Highest: the highest 5% of records. “The reason for dividing the fourth quartile into categories 3 and 4 was to distinguish the most extreme values of journey times and deprivation where the greatest effect might be expected” (Haynes *et al*, 2008).

All analyses were conducted using Intercooled Stata 11.1 for Windows (StataCorp, College Station, Texas, USA). Logistic regression was used to estimate the associations between travel time and distance and screening history and stage at diagnosis. Cox regression (Cox, 1972) was used to estimate adjusted cervical cancer mortality hazard ratios (HRs). All analyses were adjusted for ethnicity, age, registration year and SEP. In general, the findings were similar for travel time and travel distance, but these were strongly correlated with each other, and were therefore not included in the models at the same time, because of potential problems of multicollinearity. However, we did include travel time to nearest GP and travel time to nearest cancer centre in the model at the same time (when adjusting for travel time); similarly we included travel distance to nearest GP and travel distance to nearest cancer centre in the model at the same time (when adjusting for travel distance).

The New Zealand Central Ethics Committee granted ethical approval for the study (CEN/08/04/EXP).

Results

Characteristics of cervical cancer patients

There were 2,323 cases of cervical cancer registered on the NZCR between 1 January 1994 and 31 December 2005. The following exclusions were made; 17 women because their cancer registration was made on the date of the woman's death, 126 cases because they did not have a domicile code that could be assigned an NZDep2001 score, 555 because they did not have a FIGO code, and a further 31 cases because they were diagnosed after 30 June 2005 (and therefore had a potential follow-up time of less than six months); this left 1,594 women to be included in the analyses. The women that were excluded because they did not have a FIGO code had a similar ethnic and SEP distribution to the cases that did have a FIGO code (Brewer *et al*, 2010). Of the 1,594 women included in the analyses: 99.2% were diagnosed based upon the histology of the primary malignant tumour (Brewer *et al*, 2009); 1,163 (73%) identified as 'Other' ethnicity, 312 of whom died during the follow-up period, 241 (77%) due to cervical cancer, and 71 (23%) due to other causes; 292 identified as Māori ethnicity (18%), 104 of whom died, 92 (88%) due to cervical cancer, and 12 (12%) due to other causes; 59 (4%) identified as Pacific ethnicity, 20 of whom died, 20 (100%) due to cervical cancer; and, 80 (5%) identified as Asian ethnicity, 14 of whom died, 13 (93%) due to cervical cancer, and 1 (7%) due to other causes (Brewer *et al*, 2011b).

Table 5.1 shows the characteristics of the 1,594 cervical cancer cases that were included in the analyses. Overall, 5% of women were (by definition) in the highest category of travel time to the nearest GP (more than 11.07 minutes), but this varied by ethnicity ($p=0.001$) and ranged from 9.3% of Māori women to 0% of Asian women. In contrast,

no Pacific or Asian women lived in the highest category of travel time to the nearest cancer centre (more than 268 minutes) compared with 4.8% of Māori women and 5.5% of other women. Similar patterns were found for travel distance.

Screening history

Table 5.2 shows the findings for screening history. In general, both travel time and travel distance had little or no association with having ever been screened, and adjustment for travel time or distance made almost no difference to the ethnic differences in screening rates. For example, the highest category of travel time to the nearest GP had an odds ratio (OR) of 0.99 (95% confidence intervals 0.57-1.72) for having ever been screened, compared with never screened. Adjustment for travel time made little change to the OR for 'ever screened' for Māori women (a change from 0.54 to 0.55) or Pacific women (a change from 0.28 to 0.30).

Stage at diagnosis

Table 5.3 shows the findings for stage at diagnosis. Travel time to the nearest GP was non-significantly associated with late stage diagnosis (OR = 1.67, 0.95-2.94), whereas travel time to the nearest cancer centre had a non-significant negative association with late stage diagnosis (0.58, 0.30-1.13). Adjustment for travel time reduced the excess risk of late-stage diagnosis by about 7% in Māori (the OR reduced from 2.71 to 2.59, which represents a decrease of 7% in the excess relative risk) and 33% in Pacific women (the OR reduced from 1.39 to 1.26 in Pacific women). Similar findings were observed when adjusting for travel distance.

Table 5.1. Characteristics of women diagnosed with cervical cancer in New Zealand, 1994-2005

Characteristic	*Ethnicity*				*All women*
	Māori	*Pacific*	*Asian*	*Other*	
Women, n (%)	292 (18.3)	59 (3.7)	80 (5.0)	1163 (73.0)	1,594
Travel time[a] (median)					
Time to nearest GP	1.66	1.98	1.82	1.70	1.71
Time to nearest cancer centre	45.12	17.83	14.39	23.6	22.26
Travel distance[b] (median)					
Distance to nearest GP	856.53	954.59	936.84	871.87	876.71
Distance to nearest cancer centre	50995.10	14382.42	12530.42	20742.58	20742.58
Travel time[a], categorised n (% of total women of that ethnicity)					
Time to nearest GP					
Low (>0.00 - <0.98)	83 (28.4)	19 (32.2)	19 (23.8)	283 (24.3)	404 (25.4)
Medium (≥0.98 - <2.96)	131 (44.9)	29 (49.2)	50 (62.5)	580 (49.9)	790 (49.6)
High (≥2.96 - 11.07)	51 (17.5)	10 (17.0)	11 (13.8)	248 (21.3)	320 (20.1)
Highest (≥11.07)	27 (9.3)	1 (1.7)	0	52 (4.5)	80 (5.0)
Time to nearest cancer centre					
Low (>0.00 - <12.38)	45 (15.4)	13 (22.0)	33 (41.3)	306 (26.3)	397 (24.9)
Medium (≥12.38 - <94.29)	154 (52.7)	43 (72.9)	42 (52.5)	561 (48.2)	800 (50.2)
High (≥94.29 - <268.56)	79 (27.1)	3 (5.1)	5 (6.3)	232 (20.0)	319 (20.0)
Highest (≥268.56)	14 (4.8)	0	0	64 (5.5)	78 (4.9)
Travel distance[b], categorised n (% of total women of that ethnicity)					
Distance to nearest GP					
Low (>0.00 - <523.39)	78 (26.7)	18 (30.5)	18 (22.5)	284 (24.4)	398 (25.0)
Medium (≥523.39 - <1573.03)	132 (45.2)	30 (50.9)	52 (65.0)	583 (50.1)	797 (50.0)
High (≥1573.03 - <9988.50)	57 (19.5)	10 (17.0)	10 (12.5)	241 (20.7)	318 (20.0)
Highest (≥9988.50)	25 (8.6)	1 (1.7)	0	55 (4.7)	81 (5.1)
Distance to nearest cancer centre					
Low (>0.00 - <8290.68)	44 (15.1)	12 (20.3)	29 (36.3)	314 (27.0)	399 (25.0)
Medium (≥8290.68 - <114780.00)	154 (52.7)	44 (74.6)	46 (57.5)	553 (47.6)	797 (50.0)
High (≥114780.00 - <313865.20)	74 (25.3)	3 (5.1)	5 (6.3)	238 (20.5)	320 (20.1)
Highest (≥313865.20)	20 (6.9)	0	0	58 (5.0)	78 (4.9)

GP: General Practitioner. [a]Time is in minutes and fractions of minutes. [b]Distance is in metres.

Table 5.2. Screening history by ethnicity, socio-economic position, and travel time/distance

Characteristic	*Not screened*				*Ever screened*								*Total participants*		*Odds ratios for ever screened* versus *never screened*		
	No smears or only after diagnosis		*Smear only in 6 months prior to diagnosis*		*Some screening*		*Irregular screening - participation*		*Irregular screening - coverage*		*Regular screening*						
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*OR (95%)*[a]	*OR (95%)*[b]	*OR (95%)*[c]
Total	305	(19.1)	570	(35.8)	38	(2.4)	142	(8.9)	312	(19.6)	227	(14.2)	1,594	(100)			
Ethnicity																	
Māori	55	(18.8)	115	(39.4)	12	(4.1)	25	(8.6)	45	(15.4)	40	(13.7)	292	(100)	0.54 (0.40-0.73)	0.55 (0.40-0.75)	0.55 (0.40-0.75)
Pacific	21	(35.6)	23	(39.0)	3	(5.1)	3	(5.1)	4	(6.8)	5	(8.5)	59	(100)	0.28 (0.15-0.54)	0.30 (0.16-0.58)	0.30 (0.16-0.58)
Asian	17	(21.3)	38	(47.5)	0	(0.0)	4	(5.0)	15	(18.8)	6	(7.5)	80	(100)	0.42 (0.24-0.72)	0.42 (0.24-0.73)	0.43 (0.25-0.74)
Other	212	(18.2)	394	(33.9)	23	(2.0)	110	(9.5)	248	(21.3)	176	(15.1)	1,163	(100)	1.00	1.00	1.00
NZDep2001, quintiles																	
1 (least deprived)	35	(15.9)	79	(35.9)	6	(2.7)	22	(10.0)	48	(21.8)	30	(13.6)	220	(100)	1.00	1.00	1.00
2	43	(18.5)	78	(33.5)	1	(0.4)	19	(8.2)	55	(23.6)	37	(15.9)	233	(100)	1.04 (0.68-1.59)	1.02 (0.66-1.57)	1.02 (0.66-1.56)
3	64	(21.1)	95	(31.3)	9	(3.0)	27	(8.9)	58	(19.1)	51	(16.8)	304	(100)	1.04 (0.70-1.56)	0.96 (0.64-1.45)	0.99 (0.66-1.49)
4	77	(19.9)	153	(39.6)	8	(2.1)	35	(9.1)	70	(18.1)	43	(11.1)	386	(100)	0.85 (0.58-1.25)	0.79 (0.53-1.18)	0.81 (0.54-1.20)
5 (most deprived)	86	(19.1)	165	(36.6)	14	(3.1)	39	(8.6)	81	(18.0)	66	(14.6)	451	(100)	1.20 (0.82-1.77)	1.10 (0.73-1.65)	1.12 (0.75-1.68)
Travel time[d]/distance[e]																	
Time to nearest GP																	
Low	99	(24.5)	138	(34.2)	7	(1.7)	38	(9.4)	64	(15.8)	58	(14.4)	404	(100)	1.00	1.00	-
Medium	141	(17.8)	285	(36.1)	22	(2.8)	67	(8.5)	156	(19.7)	119	(15.1)	790	(100)	1.22 (0.92-1.62)	1.26 (0.95-1.68)	-
High	51	(15.9)	118	(36.9)	6	(1.9)	33	(10.3)	76	(23.8)	36	(11.3)	320	(100)	1.00 (0.71-1.42)	1.02 (0.71-1.45)	-
Highest	14	(17.5)	29	(36.3)	3	(3.8)	4	(5.0)	16	(20.0)	14	(17.5)	80	(100)	0.99 (0.57-1.72)	0.91 (0.52-1.60)	-
Time to nearest cancer centre																	
Low	74	(18.6)	141	(35.5)	5	(1.3)	38	(9.6)	76	(19.1)	63	(15.9)	397	(100)	1.00	1.00	-
Medium	157	(19.6)	306	(38.3)	24	(3.0)	69	(8.6)	149	(18.6)	95	(11.9)	800	(100)	0.88 (0.66-1.16)	0.90 (0.68-1.21)	-
High	63	(19.7)	97	(30.4)	5	(1.6)	31	(9.7)	66	(20.7)	57	(17.9)	319	(100)	1.21 (0.86-1.70)	1.31 (0.91-1.87)	-
Highest	11	(14.1)	26	(33.3)	4	(5.1)	4	(5.1)	21	(26.9)	12	(15.4)	78	(100)	1.04 (0.60-1.81)	1.09 (0.62-1.91)	-

Table 5.2. (continued) Screening history by ethnicity, socio-economic position, and travel time/distance

Characteristic	*Not screened*				*Ever screened*								*Total participants*		*Odds ratios for ever screened* versus *never screened*		
	No smears or only after diagnosis		*Smear only in 6 months prior to diagnosis*		*Some screening*		*Irregular screening - participation*		*Irregular screening - coverage*		*Regular screening*						
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*OR (95%)*[a]	*OR (95%)*[b]	*OR (95%)*[c]
Distance to nearest GP																	
Low	96	(24.1)	131	(32.9)	7	(1.8)	36	(9.0)	70	(17.6)	58	(14.6)	398	(100)	1.00	-	1.00
Medium	146	(18.3)	294	(36.9)	22	(2.8)	68	(8.5)	153	(19.2)	114	(14.3)	797	(100)	1.08 (0.82-1.43)	-	1.11 (0.84-1.48)
High	48	(15.1)	117	(36.8)	6	(1.9)	34	(10.7)	71	(22.3)	42	(13.2)	318	(100)	1.01 (0.71-1.43)	-	1.01 (0.71-1.44)
Highest	15	(18.5)	28	(34.6)	3	(3.7)	4	(4.9)	18	(22.2)	13	(16.0)	81	(100)	0.92 (0.53-1.58)	-	0.83 (0.47-1.45)
Distance to nearest cancer centre																	
Low	67	(16.8)	147	(36.8)	6	(1.5)	39	(9.8)	79	(19.8)	61	(15.3)	399	(100)	1.00	-	1.00
Medium	165	(20.7)	300	(37.6)	23	(2.9)	68	(8.5)	143	(17.9)	98	(12.3)	797	(100)	0.88 (0.66-1.17)	-	0.90 (0.67-1.21)
High	59	(18.4)	98	(30.6)	6	(1.9)	33	(10.3)	69	(21.6)	55	(17.2)	320	(100)	1.32 (0.93-1.86)	-	1.39 (0.97-1.99)
Highest	14	(17.9)	25	(32.1)	3	(3.8)	2	(2.6)	21	(26.9)	13	(16.7)	78	(100)	0.91 (0.52-1.59)	-	0.96 (0.54-1.69)

OR (95%): Odds ratio (95% confidence intervals); NZDep2001: New Zealand Deprivation Index 2001; GP: General Practitioner. [a]Adjusted for ethnicity, age, registration year and NZDep2001. [b]Adjusted for ethnicity, age, registration year, NZDep2001 and travel time. [c]Adjusted for ethnicity, age, registration year, NZDep2001 and travel distance. [d]Time is in minutes and fractions of minutes. [e]Distance is in metres.

Table 5.3. Stage at diagnosis by ethnicity and travel time/distance

	FIGO stage at diagnosis, n (%)				*ORs for late stage diagnosis (stage II-IV)* versus *early stage diagnosis (0-IB2)*		
	0-IB2	*II-IIB*	*III-IIIB*	*IVA-IVB*	*OR (95% CI)*[a]	*OR (95% CI)*[b]	*OR (95% CI)*[c]
Ethnicity							
Māori	171 (58.6)	52 (17.8)	57 (19.5)	12 (4.1)	2.71 (1.98-3.72)	2.59 (1.88-3.56)	2.64 (1.92-3.63)
Pacific	40 (67.8)	9 (15.3)	7 (11.9)	3 (5.1)	1.39 (0.76-2.54)	1.26 (0.68-2.33)	1.26 (0.68-2.33)
Asian	54 (67.5)	9 (11.3)	13 (16.3)	4 (5.0)	1.07 (0.63-1.82)	1.04 (0.61-1.78)	1.04 (0.61-1.77)
Other	818 (70.3)	172 (14.8)	142 (12.2)	31 (2.7)	1.00	1.00	1.00
NZDep2001, quintiles							
1 (least deprived)	160 (72.7)	32 (14.6)	26 (11.8)	2 (0.9)	1.00	1.00	1.00
2	172 (73.8)	32 (13.7)	23 (9.9)	6 (2.6)	0.90 (0.57-1.43)	0.95 (0.59-1.51)	0.95 (0.59-1.51)
3	205 (67.4)	46 (15.1)	41 (13.5)	12 (4.0)	1.24 (0.81-1.90)	1.29 (0.84-2.00)	1.31 (0.84-2.02)
4	250 (64.8)	64 (16.6)	61 (15.8)	11 (2.9)	1.26 (0.84-1.89)	1.34 (0.88-2.05)	1.35 (0.89-2.07)
5 (most deprived)	296 (65.6)	68 (15.1)	68 (15.1)	19 (4.2)	1.09 (0.72-1.65)	1.21 (0.78-1.86)	1.20 (0.78-1.85)
Travel time[d]/distance[e]							
Time to nearest GP							
Low	283 (70.1)	55 (13.6)	53 (13.1)	13 (3.2)	1.00	1.00	-
Medium	518 (65.6)	132 (16.7)	114 (14.4)	26 (3.3)	1.28 (0.96-1.72)	1.27 (0.94-1.71)	-
High	232 (72.5)	42 (13.1)	40 (12.5)	6 (1.9)	1.17 (0.81-1.70)	1.12 (0.77-1.64)	-
Highest	50 (62.5)	13 (16.3)	12 (15.0)	5 (6.3)	1.67 (0.95-2.94)	1.70 (0.95-3.04)	-
Time to nearest cancer centre							
Low	284 (71.5)	57 (14.4)	45 (11.3)	11 (2.8)	1.00	1.00	-
Medium	518 (64.8)	136 (17.0)	118 (14.8)	28 (3.5)	1.33 (0.99-1.79)	1.32 (0.97-1.79)	-
High	218 (68.3)	39 (12.2)	53 (16.6)	9 (2.8)	1.09 (0.75-1.57)	1.06 (0.72-1.56)	-
Highest	63 (80.8)	10 (12.8)	3 (3.9)	2 (2.6)	0.58 (0.30-1.13)	0.56 (0.29-1.10)	-
Distance to nearest GP							
Low	274 (68.8)	59 (14.8)	51 (12.8)	14 (3.5)	1.00	-	1.00
Medium	532 (66.8)	123 (15.4)	117 (14.7)	25 (3.1)	1.12 (0.83-1.49)	-	1.10 (0.82-1.48)
High	223 (70.1)	48 (15.1)	39 (12.3)	8 (2.5)	1.18 (0.82-1.70)	-	1.14 (0.79-1.67)
Highest	54 (66.7)	12 (14.8)	12 (14.8)	3 (3.7)	1.37 (0.78-2.40)	-	1.48 (0.83-2.64)

Table 5.3. (continued) Stage at diagnosis by ethnicity and travel time/distance

	FIGO stage at diagnosis, n (%)				*ORs for late stage diagnosis (stage II-IV)* versus *early stage diagnosis (0-IB2)*		
	0-IB2	*II-IIB*	*III-IIIB*	*IVA-IVB*	*OR (95% CI)*[a]	*OR (95% CI)*[b]	*OR (95% CI)*[c]
Distance to nearest cancer centre							
Low	286 (71.7)	60 (15.0)	42 (10.5)	11 (2.8)	1.00	-	1.00
Medium	515 (64.6)	133 (16.7)	121 (15.2)	28 (3.5)	1.29 (0.96-1.74)	-	1.26 (0.93-1.71)
High	223 (69.7)	38 (11.9)	51 (15.9)	8 (2.5)	0.99 (0.69-1.43)	-	0.94 (0.64-1.38)
Highest	59 (75.6)	11 (14.1)	5 (6.4)	3 (3.9)	0.77 (0.41-1.46)	-	0.72 (0.38-1.38)

FIGO: International Federation of Gynecology and Obstetrics; OR (95% CI): Odds ratio (95% confidence intervals): NZDep2001: New Zealand Deprivation Index 2001: GP: General Practitioner. [a]Adjusted for ethnicity, age, registration year and NZDep2001. [b]Adjusted for ethnicity, age, registration year, NZDep2001 and travel time. [c]Adjusted for ethnicity, age, registration year, NZDep and travel distance. [d]Time is in minutes and fractions of minutes. [e]Distance is in metres.

Mortality

Table 5.4 shows the findings for cervical cancer mortality in patients diagnosed with cervical cancer. Travel time to the nearest GP and cancer centre were only weakly and inconsistently associated with cervical cancer-specific mortality (adjusted for stage); for example, the highest category of travel time to the nearest GP had a HR of 1.32 (0.79-2.19) for mortality, whereas there was little or no association with travel time to the nearest cancer centre. Adjustment for travel time reduced the excess risk of mortality by only 3% in Māori (the HR reduced from 1.59 to 1.57) and 13% in Pacific women (the HR reduced from 1.92 to 1.80). Similar findings were observed when using travel distance rather than travel time.

Discussion

This study has found that travel time/distance is only weakly associated with cervical cancer screening, stage at diagnosis and mortality in New Zealand. However, travel time may account for a small proportion of the ethnic differences in stage at diagnosis and in mortality, particularly for Pacific women. Adjustment for travel time reduced the excess risk of late stage diagnosis by about 7% in Māori and 33% in Pacific women, and adjustment for travel time reduced the excess risk of mortality by about 3% in Māori and 13% in Pacific women. Thus, the relatively weak effects of travel time primarily affect the ethnic differences in stage at diagnosis, rather than subsequent survival (at a given stage of diagnosis).

Table 5.4. Hazard ratios for mortality by ethnicity and travel time/distance

Characteristic	*Number of deaths*	*HR (95% CI) adjusted for age, registration year, ethnicity, stage and NZDep2001*	*HR (95% CI) adjusted for age, registration year, ethnicity, stage, NZDep2001 and travel time*	*HR (95% CI) adjusted for age, registration year, ethnicity, stage, NZDep2001 and travel distance*
Ethnicity				
Māori	92	1.59 (1.21-2.08)	1.57 (1.19-2.06)	1.58 (1.20-2.07)
Pacific	20	1.92 (1.20-3.08)	1.80 (1.11-2.91)	1.90 (1.17-3.07)
Asian	13	0.70 (0.40-1.22)	0.67 (0.38-1.18)	0.68 (0.39-1.21)
Other	241	1.00	1.00	1.00
NZDep2001, quintiles				
1 (least deprived)	38	1.00	1.00	1.00
2	41	0.97 (0.62-1.51)	1.04 (0.66-1.63)	1.03 (0.65-1.62)
3	75	1.32 (0.89-1.96)	1.41 (0.94-2.11)	1.42 (0.95-2.14)
4	95	1.14 (0.78-1.66)	1.25 (0.84-1.86)	1.24 (0.83-1.85)
5 (most deprived)	117	1.15 (0.78-1.70)	1.29 (0.86-1.94)	1.25 (0.83-1.88)
Travel time[a]/distance[b]				
Time to nearest GP				
Low	85	1.00	1.00	-
Medium	193	1.13 (0.87-1.47)	1.13 (0.87-1.47)	-
High	67	1.33 (0.95-1.86)	1.33 (0.94-1.87)	-
Highest	21	1.28 (0.78-2.10)	1.32 (0.79-2.19)	-
Time to nearest cancer centre				
Low	81	1.00	1.00	-
Medium	201	1.12 (0.87-1.46)	1.08 (0.83-1.42)	-
High	71	1.03 (0.74-1.42)	0.96 (0.68-1.36)	-
Highest	13	1.02 (0.56-1.86)	0.96 (0.52-1.75)	-
Distance to nearest GP				
Low	90	1.00	-	1.00
Medium	187	0.98 (0.76-1.27)	-	0.98 (0.75-1.26)
High	72	1.23 (0.89-1.70)	-	1.23 (0.88-1.71)
Highest	17	0.93 (0.55-1.58)	-	0.95 (0.55-1.64)
Distance to nearest cancer centre				
Low	81	1.00	-	1.00
Medium	200	1.07 (0.82-1.40)	-	1.03 (0.79-1.35)
High	70	1.00 (0.72-1.38)	-	0.95 (0.67-1.34)
Highest	15	1.04 (0.59-1.84)	-	1.02 (0.57-1.81)

HR (95% CI): Hazard ratio (95% confidence intervals); NZDep2001: New Zealand Deprivation Index 2001; GP: General Practitioner. [a]Time is in minutes and fractions of minutes. [b]Distance is in metres.

One of the strengths of the current study is that the Cancer Registry Act came into effect in 1994 making cancer registration mandatory (Ministry of Health, 2010a), and case under-ascertainment unlikely (Ministry of Health, 2002). Death registration is also mandatory in New Zealand, and can be linked to cancer registrations using the NHI number; thus there is a high probability that the study identified all of the cases that died in New Zealand. There may have been some misclassification of cause of death, but it is unlikely to have produced significant bias in the ethnic comparisons (Sarfati *et al*, 2010a). Furthermore, classification of the cause of death for patients on the NZCR is highly accurate since in cases that are registered prior to death, information from the NZCR is used to classify the underlying cause of death (New Zealand Health Information Service, 2004).

This is the first study in New Zealand to measure the associations between travel time or travel distance (measured from the population weighted centroid of the CAU of residency of cervical cancer patients to the nearest GP and cancer centre), and cervical cancer-specific mortality. The few previous New Zealand studies that have examined the association between distance and cervical cancer mortality have used less precise measures of distance, such as aggregate measures based on population size (Brewer *et al*, 2011b; Brewer *et al*, 2009). Internationally, previous studies have also used less accurate methods of estimating distance/remoteness by using geometric centroids of census areas of residency (rather than population weighted centroids) and/or by estimating the travel time or distance to the centroids of census areas or to towns containing health care facilities (rather than to the specific location of a GP or cancer centre) (Jong *et al*, 2004; O'Brien *et al*, 2000; Tan *et al*, 2009). This is also the first

study in New Zealand to use more direct measures of travel time or travel distance to assess their associations with cervical screening history.

The limitations of the study include the potential misclassification of ethnicity, which has been estimated to produce a 17% undercount of Māori cancer registrations (Cormack *et al*, 2005) (this involves misclassification of ethnicity on registrations, rather than case under-ascertainment). Thus, the 'Other' ethnic group may contain some Māori cases that were incorrectly classified, thereby diluting the ethnic survival differences. There is also evidence of a 6–7% undercount of Māori deaths (Ajwani *et al*, 2003a; Cormack *et al*, 2005), but this would not bias the current study since the ethnicity recorded on the NZCR was used in all analyses. The classification of ethnicity was based on the wording of the corresponding census questions, and these have changed over time, but once again this is unlikely to have produced serious bias because the ethnicity recorded on the NZCR was also used to classify the corresponding deaths, and the analyses were adjusted for registration year. There may also be misclassification of area-based SEP, but any such misclassification is unlikely to be associated with subsequent survival and, if anything, is likely to produce underestimates of the differences in survival between the various demographic groups.

The estimates of travel time and distance are limited in their accuracy since we used domicile codes and were not able to estimate the time or distance from the patient's residential address, and we were also not able to estimate the time or distance to the actual GP surgery or cancer centre that the patient attended. Women may choose to travel to a more distant GP, but it is unlikely that they would choose to travel to a more distant cancer centre since there are only six in New Zealand. The women who choose

to travel to a more distant GP are presumably more likely to live nearby to several GPs, such that the actual time or distance travelled is not greatly different to our estimations. Thus there may be some misclassification of travel time and distance but any such misclassification is likely to be small.

The findings from previous studies of travel time and/or distance and cancer survival in New Zealand have been inconsistent. Gill & Martin (Gill and Martin, 2002) found that after adjusting for other variables, distance from a cancer centre was not associated with poorer survival from upper gastrointestinal cancers. However, the relationship was complex as they found in univariate analyses that those living 51-100 km from a cancer centre had a poorer prognosis, but this difference disappeared when adjusted for gender, age, ethnicity, and the New Zealand Deprivation Index 1996, although these analyses were not adjusted for stage/extent of disease (Gill and Martin, 2002). Haynes *et al* (Haynes *et al*, 2008) found that after adjusting for extent of disease, increasing travel time to the nearest GP was associated with poorer survival for men with prostate cancer. Travel to the nearest cancer centre was also independently associated with poorer survival for colorectal and breast cancer patients, and less consistently associated with an adverse outcome in prostate cancer patients (Haynes *et al*, 2008). In contrast, Bennett *et al* (Bennett *et al*, 2007) found that after adjustment for stage and other variables distance from a cancer centre did not affect survival of women with breast cancer. We have previously shown that urban/rural residency had only a small effect on ethnic disparities in cervical cancer survival after adjusting for other variables including stage (Brewer *et al*, 2009).

Studies in other countries have also yielded inconsistent findings. In Australia, Aboriginal women in rural and remote areas were found to have a higher risk of death from cervical cancer than Aboriginal women living in urban areas (O'Brien *et al*, 2000). The opposite pattern was observed for non-Aboriginal women. This study did not adjust for stage at diagnosis or screening history (O'Brien *et al*, 2000). More recently, Jong *et al* (Jong *et al*, 2004) were able to adjust for stage at diagnosis and found a significant increase in the relative excess risk of death for women with cervical cancer living in a remote area of New South Wales. In the USA, Tan *et al* (Tan *et al*, 2009) found, in New York state, that increasing driving time (from resident's county seat to the nearest cancer treatment centre's county seat) lead to an increase in the cervical cancer-specific death rate even when adjusting for population density. However, they were not able to adjust for stage. The pattern varied over time: in 1979 rural counties had an excess of around 1.5 deaths per 100,000 women compared with more densely populated counties, but by 2001 the rural counties had lower rates than the urban counties by roughly one death per 100,000 women (Tan *et al*, 2009). Coker *et al* (Coker *et al*, 2009a) also found significantly shorter cervical cancer-specific survival in women living in more rural areas of Texas, after adjustment for stage (as well as treatment, age, race, SEP, and cell type). When stratified by stage, the association was only significant for women with regional/distant disease (compared with localised and unknown) (Coker *et al*, 2009a).

The (weak) associations that we found between travel time and the ethnic differences in stage at diagnosis persisted after adjustment for screening history; similarly the ethnic differences in mortality persisted after adjustment for stage at diagnosis. This suggests that there may be ethnic variations in access to treatment or in treatment quality, which in turn may be related to travel time (Jong *et al*, 2004). There is some evidence for

variation in treatment quality (Davis *et al*, 2006; Rumball-Smith, 2009; Tobias and Yeh, 2007) and disease management (Stevens *et al*, 2008b) in New Zealand. However, the only study to date to examine potential treatment differences and their possible impact on cervical cancer-specific survival in New Zealand found that there were no differences in receipt of total/radical hysterectomy or brachytherapy between Māori and non-Māori after adjusting for age and stage of disease (excluding those with unknown stage) (McLeod *et al*, 2010). The study was not able to examine treatments such as external beam radiotherapy or chemotherapy which are generally provided on an outpatient basis (McLeod *et al*, 2010).

Conclusions

In summary, we assessed the associations of travel time and distance with cervical cancer screening, stage at diagnosis and mortality. In general, we found that both travel time and distance are only weakly associated with these outcomes. However, travel time may account for a small proportion of the ethnic differences in stage at diagnosis and mortality, particularly for Pacific women. These relatively weak effects of travel time primarily affect stage at diagnosis, rather than subsequent survival (at a given stage of diagnosis). It is possible that other factors may play a role, including differences in treatment and follow-up.

CHAPTER 6

Which factors account for the ethnic inequalities in stage at diagnosis and cervical cancer survival in New Zealand?

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The study assessed what proportions of the substantial ethnic inequalities in late stage diagnosis and cervical cancer survival in New Zealand were due to factors such as screening history, stage at diagnosis, comorbid conditions, and travel time to the nearest General Practitioner and cancer centre. The study involved 1,594 cervical cancer cases registered between 1994 and 2005. G-computation was used to evaluate the validity of the estimates obtained by standard regression methods. Māori and Pacific women had a higher risk of late-stage diagnosis compared with 'Other' women with adjusted odds ratios of 2.39 (95% confidence intervals: 1.72, 3.30), and 1.06 (0.57, 1.96) respectively. Adjusted hazard ratios of mortality for cervical cancer for Māori and Pacific women were 1.45 (1.10, 1.92) and 1.55 (0.93, 2.57) respectively. G-computation analyses gave similar findings, supporting the view that the standard methods used provided valid estimates. The excess relative risk of late-stage diagnosis in Māori women remains largely unexplained, whereas in Pacific women it is almost entirely due to ethnic differences in screening history and travel time. More than one-half of the excess relative risk of mortality in Māori and Pacific women is explained by differences in stage at diagnosis and comorbid conditions.

Submitted

Introduction

It is well-established that there are major ethnic inequalities in cervical cancer screening (Brewer *et al*, 2010), stage at diagnosis (Brewer *et al*, 2009) and mortality in New Zealand (Brewer *et al*, 2009; Priest *et al*, 2010), but the reasons for these differences are unclear. In particular the increased risk of mortality in Māori and Pacific women is only partially explained by adjustment for stage at diagnosis, socio-economic position (SEP), and urban/rural residency. These patterns have varied over time, with post-diagnostic factors playing an important role in the high Māori mortality rates in the 1990s, but in more recent years the excess mortality in Māori women appeared to be almost entirely due to stage at diagnosis (Brewer *et al*, 2009). Ethnic differences in stage at diagnosis are not entirely explained by differences in screening history (Brewer *et al*, 2010). Adjustment for comorbid conditions accounts for only a moderate proportion of the ethnic differences in mortality (Brewer *et al*, 2011b). In a separate analysis (Brewer *et al*, 2011a), we found that travel time and distance were only weakly associated with cervical cancer screening, stage at diagnosis and mortality in New Zealand. However, travel time may account for a small proportion of the ethnic differences in stage at diagnosis, and to a lesser extent mortality, particularly for Pacific women.

To further explore the reasons for the ethnic differences in mortality from cervical cancer, we have further analyzed the New Zealand data to understand the relative importance, with regard to cervical cancer stage at diagnosis and subsequent survival, of various factors (screening history, stage at diagnosis, comorbid conditions, and travel time to the nearest General Practitioner (GP) or cancer centre) which have previously been considered separately (Brewer *et al*, 2011a; Brewer *et al*, 2011b; Brewer *et al*,

2010; Brewer *et al*, 2009). Furthermore, we examined the direct effects of ethnicity on stage and mortality after taking into account possible mediators, such as screening history and comorbidity.

Materials and Methods

The New Zealand Central Ethics Committee granted ethical approval for the study (CEN/08/04/EXP).

Study population and risk factors

The population comprised all cervical cancer cases registered with the New Zealand Cancer Registry (NZCR) between 1 January 1994 and 31 December 2005 (Brewer *et al*, 2011a; Brewer *et al*, 2011b; Brewer *et al*, 2010; Brewer *et al*, 2009). The NZCR records self-identified ethnicity, and allows for multiple responses. Participants who reported more than one ethnicity were classified into a single ethnicity using the standard system of prioritisation: Māori>Pacific>Asian>'Other' (New Zealand Department of Statistics, 1990). Participants with missing ethnicity data were included in the 'Other' (predominantly European) ethnic group. This approach is standard practice in New Zealand health research (Ministry of Health, 2002; Ministry of Health, 2006). All registrations include the National Health Index (NHI) number which uniquely identifies individual health care users; this was used to obtain cause-specific mortality data (from the Mortality Collection) up to the end of December 2005 (the most recent year for which data was available), hospital events data (from the National Minimum Dataset (NMDS)) from 1988 to 31 December 2005, and the women's cervical screening history

from the National Cervical Screening Programme-Register from 1986 to 31 December 2006.

SEP was estimated using the New Zealand Deprivation Index 2001 (NZDep2001), an area-based measure derived from a combination of nine socioeconomic variables derived from the national census (Crampton *et al*, 2004). Each participant was assigned a score based upon the residential area (the domicile code) in which they lived, as recorded on the NZCR at the time of registration. These scores were then grouped into quintiles (Crampton *et al*, 2004).

Data on stage at diagnosis were obtained from the NZCR, and reported using the International Federation of Gynecology and Obstetrics (FIGO) (Benedet *et al*, 2006) classification. In order to provide sufficient numbers in each category, the FIGO stages were grouped into four categories: stages 0-IB2; II-IIB; III-IIIB; IVA-IVB. Women with an unknown stage at diagnosis, or who could not be allocated a deprivation score, were excluded from the analyses. There was little ethnic or socioeconomic difference in the percentage of cases with missing FIGO codes (Brewer *et al*, 2010).

The classifications of screening history were based on those used for the New Zealand Cervical Cancer Audit (Sadler *et al*, 2004) and for quality monitoring by the National Cervical Screening Programme (Ministry of Health, 2000). Women were categorized as ‘not screened’ or ‘ever screened’. We excluded all of the smears taken in the six months immediately prior to diagnosis since some of these will have been taken for diagnostic, not screening, purposes (Sasieni *et al*, 2003; Spayne *et al*, 2007). The full details of the categorization have been described elsewhere (Brewer *et al*, 2010). Cervical screening

guidelines are extremely complex (National Screening Unit, 2008), and the categories used in this study are therefore only able to approximate the women's screening histories (Sadler *et al*, 2004).

Comorbidity was assessed using the hospital events data, according to the coding algorithms of Quan *et al* (Quan *et al*, 2005) for the Charlson Comorbidity Index (CCI) (Charlson *et al*, 1987) and the Elixhauser instrument (Elixhauser *et al*, 1998). Our previous analyses (Brewer *et al*, 2011b) identified 12 important comorbid conditions (congestive heart failure, valvular disease, complicated hypertension, chronic pulmonary disease, complicated diabetes, renal failure, liver disease, coagulopathy, obesity, fluid and electrolyte disorders, blood loss anaemia, and drug abuse) which, when adjusted for concurrently, had a stronger confounding effect than either the Elixhauser instrument or the CCI on cervical cancer-specific mortality by ethnicity. We therefore concurrently adjusted for these 12 comorbid conditions.

The methods used to estimate travel time and distance to the nearest GP and cancer centre were based on those of Haynes *et al (Haynes et al, 2008)* and Pearce *et al* (Pearce *et al*, 2006). The travel time (in minutes, and fractions of minutes) and distance (in metres) to the nearest GP surgery, and the nearest of the six cancer centres, were calculated, using a geographical information system (Pearce *et al*, 2006). Our previous analyses (Brewer *et al*, 2011a) showed similar findings for travel time and travel distance, and in the current analyses we therefore adjusted only for travel time. The travel times were categorized according to the method of Haynes *et al* (Haynes *et al*, 2008): Low: the lowest quartile using the whole sample; Medium: quartiles two and

three, incorporating half the records around the median; High: records between the 75 and 95 percentiles; Highest: the highest 5% of records.

Data analysis

Logistic regression was used to estimate associations between screening history, travel time and stage at diagnosis. Cox proportional hazards (Cox, 1972) was used to estimate cause-specific hazard ratios (HRs) for cervical cancer mortality associated with stage at diagnosis, comorbid conditions, and travel time. Since we analyzed cervical cancer specific mortality with deaths for other causes being competing events (Crowder, 2001; Putter *et al*, 2007), we also conducted a Fine and Gray model (Fine and Gray, 1999) to understand whether the effects observed on the HR scale were maintained on the cumulative incidence scale. The estimates obtained from Cox regression and Fine and Gray were consistent and we therefore report only those from Cox regression.

All analyses were adjusted for age, registration year, and SEP.

We also estimated the proportions of the observed ethnic differences in risk that could not be attributed to the mediating variables. The variables involved in these analyses are shown in the form of Directed Acyclic Graphs (DAGs) in Figure 6.1 (stage and diagnosis) and Figure 6.2 (cervical cancer survival). We were interested in what proportion of the ethnic differences in stage at diagnosis could not be attributed to differences in screening, and what proportion of the ethnic differences in mortality could not be attributed to stage at diagnosis and comorbidity. The simplest way to do this is to estimate relative risks (odds ratio (OR) or HR) with and without adjustment for potential mediating variables. These can then be used to estimate the direct effect, *i.e.*

what proportion of the ethnic differences is not explained by these mediators as opposed to the indirect effect that is the proportion explained by the mediators. However, under some circumstances, standard regression models may fail to correctly estimate direct and indirect effects. Simple adjustment for the mediator can give misleading results if there is an interaction between the exposure of interest and the mediator, or if there are confounders of the mediator-outcome relationship (Cole and Hernan, 2002). In the present setting, the time that it takes for a woman to travel to a health centre would be an example of a potential confounder of the relationship between screening and stage at diagnosis (Figure 6.1). Even when measured, standard adjustment for mediator-outcome confounders fails to correctly partition the total effect into its direct and indirect components if these confounders are themselves affected by the exposure. For example, ethnicity may affect place of residency, and hence the travel time to the health centre. In these circumstances the G-computation method can be used to obtain estimates of the direct and indirect effects under less restrictive assumptions than are needed for standard analyses (Daniel *et al*, 2010; Petersen *et al*, 2006).

We therefore used G-computation in addition to standard regression methods. Since G-computation is implemented on the absolute risk scale (*i.e.* risk difference), and therefore is not used for survival analysis which involves a relative risk scale, we compared three estimates: i) excess relative risk estimates (OR or HR) obtained from log-linear models (logistic regression, Cox regression); ii) risk difference estimates obtained from log-binomial regression; and iii) risk differences obtained from G-computation. As noted above, we carried out two separate analyses, namely: i) the effect of Māori ethnicity on tumour stage, with screening as the mediator, and ii) the effect of Māori ethnicity on mortality, with comorbidity and stage, as the mediators. In each

instance we compared Māori with 'Other' ethnicity, and Asian and Pacific participants were excluded because their numbers were too small. To obtain comparable estimates between the G-computation and the standard approach, we adjusted for age and registration year in all models, and we included SEP and travel time to the nearest GP and cancer centre in the G-computation estimate only as exposure-dependent confounders of the mediator-outcome associations, not as mediators of interest themselves. This implies that, in these sensitivity analyses, the direct effects of ethnicity on stage include all paths from ethnicity to stage except for those going through screening (Figure 6.1), and the direct effects of ethnicity on survival include all paths except those mediated by comorbidity and stage (Figure 6.2 (note: here screening is assumed to affect mortality only through stage)). In the analyses in which survival is the outcome of interest we used: i) time to event of interest as the outcome in Cox regression by censoring individuals at three-year survival after diagnosis and by excluding from the analyses the 3% of women who were censored before the three years of follow-up, because of loss to follow-up or death from causes other than cervical cancer; and ii) three-year survival as a binary outcome in the log-binomial regression and G-computation. Furthermore we restricted the analyses to women diagnosed before December 2002 (*i.e.* at least three years before the administrative end of the follow-up in December 2005). Hence the mediation analysis was based on 1,204 women.

Analyses were conducted using Intercooled Stata 11 for Windows (StataCorp, College Station, Texas, USA).

Figure 6.1. Directed acyclic graph (DAG) showing the association between ethnicity and stage (corresponds to Table 6.2)

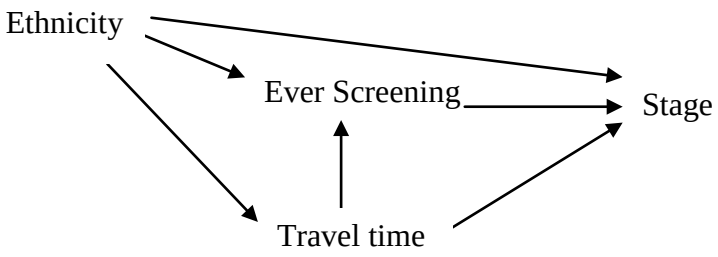
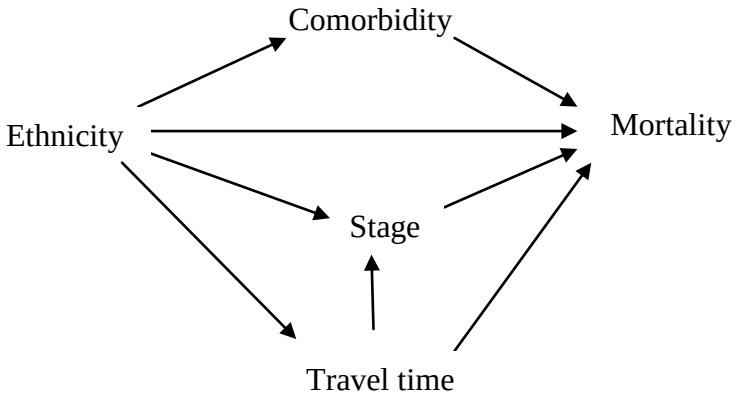


Figure 6.2. Directed acyclic graph (DAG) showing the association between ethnicity and mortality (corresponds to Table 6.3)



Results

Characteristics of cervical cancer patients

There were 2,323 cases of cervical cancer registered on the NZCR between 1 January 1994 and 31 December 2005. The following exclusions were made: 621 because they did not have a FIGO code (including 17 women whose cancer registration was made on the date of the their death, and 50 women that could not be assigned an NZDep2001 score), 77 cases because they did not have a domicile code that could be assigned an NZDep2001 score, and a further 31 cases because they were diagnosed after 30 June 2005 (this date was chosen to ensure that all women had potential follow-up of at least six months). This left 1,594 women to be included in the analyses, whose characteristics are reported in Table 6.1. The women who were excluded because they did not have a FIGO code had a similar ethnic and SEP distribution to the cases who did have a FIGO code (Brewer *et al*, 2010). Of the 1,594 women included in the analyses: 99.2% had a histologically confirmed diagnosis; 1,163 (73%) identified as 'Other' ethnicity, 312 of whom died during the follow-up period (77% due to cervical cancer, and 23% due to other causes); 292 identified as Māori ethnicity (18%), 104 of whom died (88% due to cervical cancer and 12% due to other causes); 59 (4%) identified as Pacific ethnicity, 20 of whom died (100% due to cervical cancer); and, 80 (5%) identified as Asian ethnicity, 14 of whom died (93% due to cervical cancer and 7% due to other causes).

Table 6.1. Characteristics of 1,594 women, by ethnicity

Characteristic	*Ethnicity*				
	Number (%)				
	Other	*Māori*	*Pacific*	*Asian*	*Total*
	1,163 (72.96)	292 (18.32)	59 (3.70)	80 (5.02)	1,594 (100.00)
Age					
≤36	318 (27.34)	82 (28.08)	10 (16.95)	12 (15.00)	422 (26.47)
>36-≤45	264 (22.70)	94 (32.19)	17 (28.81)	19 (23.75)	394 (24.72)
>45-≤59	262 (22.53)	78 (26.71)	23 (38.98)	23 (28.75)	386 (24.22)
>59	319 (27.43)	38 (13.01)	9 (15.25)	26 (32.50)	392 (24.59)
Registration year					
1994-1997	386 (33.19)	115 (39.38)	24 (40.68)	19 (23.75)	544 (34.13)
1998-2002	498 (42.82)	112 (38.36)	17 (28.81)	32 (40.00)	659 (41.34)
2002-2005	279 (23.99)	65 (22.26)	18 (30.51)	29 (36.25)	391 (24.53)
Screening					
Never screened	606 (52.11)	170 (58.22)	44 (74.58)	55 (68.75)	875 (54.89)
Ever screened	557 (47.89)	122 (41.78)	15 (25.42)	25 (31.25)	719 (45.11)
Stage					
0–IB2	818 (70.34)	171 (58.56)	40 (67.80)	54 (67.50)	1,083 (67.94)
II–IIB	172 (14.79)	52 (17.81)	9 (15.25)	9 (11.25)	242 (15.18)
III–IIIB	142 (12.21)	57 (19.52)	7 (11.86)	13 (16.25)	219 (13.74)
IVA–IVB	31 (2.67)	12 (4.11)	3 (5.08)	4 (5.00)	50 (3.14)
Comorbidity[a]					
Absence	1,105 (95.01)	262 (89.73)	49 (83.05)	74 (92.50)	1,490 (93.48)
Presence	58 (4.99)	30 (10.27)	10 (16.95)	6 (7.50)	104 (6.52)
SEP					
1 (least deprived)	194 (16.68)	12 (4.11)	1 (1.69)	13 (16.25)	220 (13.80)
2	189 (16.25)	19 (6.51)	9 (15.25)	16 (20.00)	233 (14.62)
3	239 (20.55)	41 (14.04)	7 (11.86)	17 (21.25)	304 (19.07)
4	298 (25.62)	62 (21.23)	11 (18.64)	15 (18.75)	386 (24.22)
5 (most deprived)	243 (20.89)	158 (54.11)	31 (52.54)	19 (23.75)	451 (28.29)
Travel time to nearest GP					
Low	283 (24.33)	83 (28.42)	19 (32.20)	19 (23.75)	404 (25.35)
Medium	580(49.87)	131 (44.86)	29 (49.15)	50 (62.50)	790 (49.56)
High	248 (21.32)	51 (17.47)	10 (16.95)	11 (13.75)	320 (20.08)
Highest	52 (4.47)	27 (9.25)	1 (1.69)	0 (0.00)	80 (5.02)
Travel time to nearest cancer centre					
Low	306 (26.31)	45 (15.41)	13 (22.03)	33 (41.25)	397 (24.91)
Medium	561 (48.24)	154 (52.74)	43 (72.88)	42 (52.50)	800 (50.19)
High	232 (19.95)	79 (27.05)	3 (5.08)	5 (6.25)	319 (20.01)
Highest	64 (5.50)	14 (4.79)	0 (0.00)	0 (0.00)	78 (4.89)

[a] Comorbidity: the presence or absence of one of the 12 comorbid conditions listed in the *'Materials and Methods*' section. SEP: socioeconomic position (New Zealand Deprivation Index 2001, in quintiles); GP: General Practitioner.

Stage at diagnosis

Table 6.2 shows the findings for stage at diagnosis. Māori and Pacific women had a higher risk of late-stage diagnosis compared with 'Other' women with an unadjusted OR of 2.71 (95% confidence intervals: 1.98-3.72) and 1.39 (0.76-2.54) respectively. After adjustment for screening history and travel time to the nearest GP and cancer centre, the OR in Māori women decreased to 2.39 (1.72-3.30), whereas the OR in Pacific women fell to 1.06 (0.57-1.96).

The ethnic-specific ORs differed by time period of diagnosis. For cases diagnosed in 1994-1997, Māori women (compared with 'Other' women) had an age, registration year, and SEP adjusted OR of 3.21 (1.92-5.35) which decreased to 2.89 (1.71-4.92) when further adjusted for screening history and travel time. For cases in Māori women diagnosed in 1998-2001 the ORs decreased from 2.79 (1.66-4.69) to 2.70 (1.57-4.65). In contrast, in 2002-2005 screening history and travel time accounted for a larger proportion of the OR in Māori women: the age, registration year, and SEP adjusted OR of 2.22 (1.15-4.29) fell to 1.70 (0.84-3.45). Adjustment for screening history and travel time accounted for differing proportions of the ORs in Pacific and Asian women in each time period, but the numbers involved were small and the confidence intervals were correspondingly wide.

Table 6.2. Odds ratios for late stage diagnosis (FIGO stages II-IV) by ethnicity

Characteristic	*Time period*			*Total*	*Adjusted for*
	1994 - 1997	1998 - 2001	2002 - 2005		
Women, n	544	659	391	1,594	
Ethnicity					
Other	1.00	1.00	1.00	1.00	Age, registration year, SEP
Māori	3.21 (1.92-5.35)	2.79 (1.66-4.69)	2.22 (1.15-4.29)	2.71 (1.98-3.72)	
Pacific	1.58 (0.60-4.13)	1.53 (0.51-4.58)	1.23 (0.39-3.88)	1.39 (0.76-2.54)	
Asian	0.93 (0.32-2.72)	1.46 (0.65-3.26)	0.81 (0.31-2.12)	1.07 (0.63-1.82)	
Ethnicity					
Other	1.00	1.00	1.00	1.00	Age, registration year, SEP, and ever *vs* never screened
Māori	2.86 (1.70-4.82)	2.76 (1.62-4.71)	1.96 (0.99-3.88)	2.50 (1.81-3.45)	
Pacific	1.33 (0.50-3.50)	1.38 (0.46-4.11)	0.97 (0.30-3.16)	1.15 (0.63-2.12)	
Asian	0.90 (0.30-2.64)	1.41 (0.63-3.19)	0.59 (0.22-1.56)	0.95 (0.56-1.62)	
Ethnicity					
Other	1.00	1.00	1.00	1.00	Age, registration year, SEP, ever *vs* never screened, and travel time to nearest GP and cancer centre
Māori	2.89 (1.71-4.92)	2.70 (1.57-4.65)	1.70 (0.84-3.45)	2.39 (1.72-3.30)	
Pacific	1.32 (0.49-3.53)	1.31 (0.43-4.03)	0.81 (0.24-2.70)	1.06 (0.57-1.96)	
Asian	0.86 (0.29-2.53)	1.36 (0.58-3.16)	0.59 (0.22-1.59)	0.92 (0.54-1.59)	

FIGO: International Federation of Gynecology and Obstetrics; SEP: Socioeconomic position; GP: General Practitioner.

Mortality from cervical cancer

Table 6.3 shows the findings for cervical cancer mortality. The HRs for Māori and Pacific women were 2.10 (1.61-2.73) and 1.96 (1.23-3.13) respectively; these fell to 1.45 (1.10-1.92) and 1.55 (0.93-2.57) respectively when adjusted for stage at diagnosis, comorbid conditions, and travel time.

The ethnic-specific HRs differed by time period of diagnosis. For cases diagnosed between 1994-1997 Māori women (compared with 'Other' women) had an age-, registration-year-, and SEP-adjusted HR of 2.47 (1.72-3.54) which fell to 1.87 (1.25-2.80) when further adjusted for stage, comorbid conditions, and travel time. For cases in Māori women diagnosed in 1998-2001, the HRs decreased from 1.81 (1.14-2.88) to 1.10 (0.66-1.85), and for cases diagnosed in 2002-2005 stage, comorbid conditions and travel time seemed to account for all of the excess risk in Māori women: the age-, registration-year-, and SEP-adjusted HR of 1.44 (0.69-3.02) fell to 0.85 (0.35-2.09). Adjustment for stage, comorbid conditions, and travel time accounted for differing proportions of the excess risk in Pacific and Asian women in each time period, but the numbers involved were small and the confidence intervals were correspondingly wide.

To check whether the different findings in the different time periods of diagnosis were due to participants who were registered in the earlier time period having longer follow-up times, we conducted a further analysis (not shown) in which we restricted the length of follow-up of cases registered during the first time period; we considered women diagnosed from 1 January 1994 to 30 June 1997 (so that all women had the opportunity of at least six months follow-up, as was the case for women registered during 2002-

2005) and censored them at 31 December 1997. This yielded very similar patterns to those shown in Table 6.3.

Mediation analysis

The findings from the standard analyses broadly agree with those from the G-computation (Table 6.4). For example, when stage was considered as the outcome and the analyses were adjusted for age and registration year, it was found that 92% of the excess relative risk was a direct effect (unmediated by screening history); the corresponding estimates for the risk difference and G-computation models were 87% and 89% respectively. Similarly, when survival was considered as the outcome, 30% of the excess relative risk in Māori was a direct effect (unmediated by comorbid conditions and stage at diagnosis); the corresponding estimates for the risk difference and G-computation analyses were 21% and 23% respectively.

Table 6.3. Hazard ratios for mortality by ethnicity

Characteristic	*Time period*			*Total*	*Adjusted for*
	1994 - 1997	1998 - 2001	2002 - 2005		
Women, n	544	659	391	1,594	
Deaths, n	176	138	52	366	
Ethnicity					
Other	1.00	1.00	1.00	1.00	Age, registration year, SEP
Māori	2.47 (1.72-3.54)	1.81 (1.14-2.88)	1.44 (0.69-3.02)	2.10 (1.61-2.73)	
Pacific	1.65 (0.82-3.33)	1.66 (0.67-4.10)	3.44 (1.36-8.72)	1.96 (1.23-3.13)	
Asian	0.29 (0.07-1.18)	1.55 (0.78-3.08)	0.64 (0.15-2.68)	0.82 (0.47-1.44)	
Ethnicity					
Other	1.00	1.00	1.00	1.00	Age, registration year, SEP, and stage
Māori	1.93 (1.32-2.83)	1.09 (0.67-1.76)	0.84 (0.36-1.95)	1.59 (1.21-2.08)	
Pacific	1.65 (0.80-3.38)	1.46 (0.58-3.65)	4.70 (1.77-12.51)	1.92 (1.20-3.08)	
Asian	0.24 (0.06-0.97)	1.31 (0.66-2.61)	0.72 (0.17-3.13)	0.70 (0.40-1.22)	
Ethnicity					
Other	1.00	1.00	1.00	1.00	Age, registration year, SEP, stage, and 12 comorbidities
Māori	1.85 (1.25-2.74)	1.01 (0.61-1.67)	0.92 (0.38-2.23)	1.45 (1.10-1.91)	
Pacific	1.63 (0.79-3.36)	1.27 (0.49-3.28)	3.38 (0.90-12.72)	1.59 (0.96-2.62)	
Asian	0.21 (0.05-0.90)	1.31 (0.65-2.64)	0.45 (0.06-3.20)	0.62 (0.35-1.11)	
Ethnicity					
Other	1.00	1.00	1.00	1.00	Age, registration year, SEP, stage, 12 comorbidities, and travel time to nearest GP and cancer centre
Māori	1.87 (1.25-2.80)	1.10 (0.66-1.85)	0.85 (0.35-2.09)	1.45 (1.10-1.92)	
Pacific	1.58 (0.75-3.33)	1.30 (0.48-3.49)	2.84 (0.68-11.90)	1.55 (0.93-2.57)	
Asian	0.21 (0.05-0.92)	1.11 (0.53-2.31)	0.70 (0.09-5.48)	0.59 (0.33-1.07)	

SEP: Socioeconomic position; GP: General Practitioner.

Table 6.4. Direct effects of Māori ethnicity *versus* 'Other' ethnicity (Asian and Pacific women excluded) on tumour stage (high *versus* low) and three-year survival, estimated using standard regression models and G-computation

	Excess risk	*Risk difference*	*G-computation*
Tumour stage as the outcome			
Total effect	1.56 (0.89, 2.46)[a]	0.16 (0.11, 0.22)[a]	0.19 (0.12, 0.25)[a]
Direct effect	1.43 (0.78, 2.31)[b]	0.14 (0.09, 0.20)[b]	0.17 (0.11, 0.24)[c]
Direct/total effect	92%	87%	89%
Three-year survival as the outcome			
Total effect	1.11 (0.59, 1.79)[a]	0.14 (0.08, 0.20)[a]	0.13 (0.05, 0.20)[a]
Direct effect	0.33 (0.00, 0.78)[d]	0.03 (-0.01, 0.07)[d]	0.03 (-0.03, 0.09)[e]
Direct/total effect	30%	21%	23%

[a]Adjusted for age and registration year. [b]Adjusted for age, registration year, and screening history (categorised as ever *versus* never screened). [c]Adjusted for age, registration year, and screening history as a mediator, and socio-economic position and travel time to the nearest General Practitioner and cancer centre as confounders of the mediator-outcome association. [d]Adjusted for age, registration year, stage (categorised as late *versus* early), and comorbid conditions (categorised as present *versus* absent). [e]Adjusted for age, registration year, with stage and comorbid conditions as mediators, and socio-economic position and travel time to the nearest General Practitioner and cancer centre as confounders of the mediators-outcome associations.

Discussion

We have previously reported that there are major ethnic differences in cervical cancer stage at diagnosis and survival in New Zealand, particularly between Māori and the 'Other' ethnic group (Brewer *et al*, 2010; Brewer *et al*, 2009). There are a number of possible factors that may contribute to these differences, including SEP (Brewer *et al*, 2009), screening history (Brewer *et al*, 2010), stage at diagnosis (Brewer *et al*, 2009), comorbid conditions (Brewer *et al*, 2011b), and travel time or distance to the nearest GP and cancer centre (Brewer *et al*, 2011a). We reported these findings separately (Brewer *et al*, 2011a; Brewer *et al*, 2011b; Brewer *et al*, 2010; Brewer *et al*, 2009), including detailed discussions of the strengths and possible limitations of this data. Briefly, the data used have a number of strengths including the fact that cancer registration and death registration are mandatory in New Zealand, and the classification of cause of death is generally very accurate for cancer cases. Possible limitations include the fact that only 73% of cases had a FIGO code recorded, and the possible misclassification of ethnicity, stage at diagnosis, and comorbid conditions, but none of these limitations appear likely to cause bias strong enough to explain our findings (Brewer *et al*, 2011a; Brewer *et al*, 2011b; Brewer *et al*, 2010; Brewer *et al*, 2009).

Here, we have considered both of the outcomes (late-stage diagnosis, and survival) and all of the possible explanatory variables (as listed above) for which information was available. As well as standard regression analyses, we used the G-computation method to assess the role of mediating variables. The findings from the standard analyses broadly agree with those using the G-computation method, indicating that the standard methods used provide reliable estimates of the proportions of the excess relative risks in

Māori that are mediated or not mediated through factors such as screening history, stage at diagnosis and comorbidity. In this case, the similarity of the findings is due to the relatively weak confounding effects of the mediator-outcome confounders included. It is important to note that if stronger mediator-outcome confounders exist but are unmeasured, then the G-computation method would suffer from similar biases and would lead to similarly misleading effect estimates as the standard regression methods.

Since the findings from the standard analyses broadly agree with those from the G-computation method, we will focus on discussing the findings obtained using standard regression methods.

Māori and Pacific women had a higher risk of late-stage diagnosis compared with 'Other' women. In Pacific women, but not in Māori women, this excess risk is almost entirely explained by screening history and travel time – the excess relative risk in Maori women fell by only 19% (*i.e.* the HR fell from 2.71 to 2.39, which represents a fall in the excess relative risk from 1.71 to 1.39), whereas that in Pacific women fell by 85%, when adjusted for these factors. The increased risk in Māori women has reduced slightly with time but is still present in the most recent cohort. The reasons for these findings are unclear. Possible explanations may include delayed diagnosis. The reasons for delayed diagnosis and non-participation in screening are complex, but may include barriers to accessing health care (such as language, culture, income and/or education level, and patient-doctor relationship) (Downs *et al*, 2008). There is also some evidence that, in New Zealand, racial discrimination is associated with poorer self-rated health (Harris *et al*, 2006a; Harris *et al*, 2006b), but there appears to be no evidence directly related to the cervical cancer care pathway. There is some evidence (Brewer *et al*,

2007b; Brewer *et al*, 2008a; Brewer *et al*, 2008b; Coppell, 2006a; Coppell, 2006b; Independent Monitoring Group of the National Cervical Screening Programme, 2004) that histological test results for Māori and Pacific women have been reported after a longer period of time than those for non-Māori, non-Pacific women, although it is unclear whether this time difference would actually lead to a later stage at diagnosis since the precursor lesions are known to exist for several years. Failure to be invited or to return for a repeat smear after an unsatisfactory result, or to have a histological specimen taken after a high grade smear, or a delay in seeing a gynaecologist, as well as not reporting symptoms, may also lead to a delay resulting in a later stage at diagnosis (Brewer *et al*, 2007b; Brewer *et al*, 2008a; Brewer *et al*, 2008b; Coppell, 2006a; Coppell, 2006b; Independent Monitoring Group of the National Cervical Screening Programme, 2004; Ratima *et al*, 1993).

In contrast with the findings for stage at diagnosis, more than half of the excess relative risk of mortality in Māori and Pacific women with cervical cancer is explained by these measured mediators, particularly stage at diagnosis and comorbid conditions – the excess relative risks for Māori and Pacific women fell by 59% (95% confidence intervals: 29% – 88%) and 43% (95% confidence intervals: -190% – 275%) respectively when adjusted for the measured mediators. Given the difficulties of identifying and correctly classifying comorbid conditions using hospital admission data, it is likely that these figures are underestimates, and that the ethnic differences in cervical cancer survival could be reduced substantially by improvements in early stage diagnosis, and better management of comorbid conditions. This may have already started to occur in New Zealand, as we found that the excess risk in Māori women decreased with time and was entirely explained by stage in the more recent cohorts.

Conclusions

In conclusion, there are major ethnic differences in cervical cancer stage at diagnosis and survival in New Zealand. The excess risk of late stage diagnosis in Māori women remains largely unexplained, whereas that in Pacific women is almost entirely due to differences in screening history and travel time. About half of the excess risk of mortality in Māori and Pacific women is explained by differences in stage at diagnosis and comorbid conditions; it is possible that other factors, including possible differences in treatment and follow-up, also play a role.

CHAPTER 7

Discussion and conclusions

For this thesis, I have conducted a series of studies of demographic differences in stage at diagnosis and subsequent survival of cervical cancer in New Zealand, and the factors that contribute to these differences. The major demographic differences are by ethnicity, which is therefore the focus of this final chapter. The differences by socioeconomic position (SEP) and urban/rural residency were relatively small. I start by briefly summarising the main findings and then discuss some of the methodological issues and limitations of these studies, and make recommendations for further research.

Main findings

1. There are major ethnic differences in cervical cancer survival in New Zealand. These are only partly explained by stage at diagnosis and differed by time period (Chapter 2).

After adjustment for stage at diagnosis, Māori ethnicity was still a major determinant of cervical cancer survival in 1994-1997, but not in later years (1998-2001 and 2002-2005). Pacific women in all three time periods had higher death rates than the other ethnicities, but the numbers were relatively small, meaning that the results should be interpreted with caution. SEP and urban/rural residency had relatively weak independent associations with mortality. For the earlier time period (1994-1997), both the measured pre-diagnostic (screening, stage) and unmeasured (in Chapter 2) post-diagnostic factors contributed to the Māori/'Other' differences in survival, whereas in the later time period (2002-2005) the differences were almost entirely due to pre-

diagnostic factors. In contrast, the corresponding analyses for Pacific cases indicated that post-diagnostic factors remain important, even in the most recent time period.

2. Regular screening is strongly protective against being diagnosed at a late stage. However, screening history does not appear to explain the ethnic differences in stage at diagnosis (Chapter 3). The findings again differed by ethnic group. The odds ratio (OR) for a late-stage diagnosis in Māori women (compared with 'Other' women) decreased only slightly when adjusted for screening history, whereas the non-significantly increased risk of late-stage diagnosis in Pacific women (compared with 'Other' women) disappeared when adjusted for screening history. Thus, there is a large excess risk of late-stage diagnosis in Māori women which is *not* explained by differences in screening history, whereas there is a small excess risk of late stage diagnosis in Pacific women which *is* explained by differences in screening history. More generally, over half of the cervical cancer cases of any ethnicity diagnosed during 1994-2005 had not been 'ever screened'; of these, 34.7% had had a 'pre-diagnostic screen' only, and 22.0% had not been screened at all prior to diagnosis. Only 14.0% of the cervical cancer cases of any ethnicity had been 'regularly' screened, 18.3% met the criteria for 'irregular screening – coverage', 8.5% were irregularly screened 'participation', and 2.5% had 'some screening'.

3. Comorbidity (a post-diagnostic factor) is associated with cervical cancer-specific survival in New Zealand. However, it accounts for only a moderate proportion of the ethnic differences in survival (Chapter 4). Women who had an Elixhauser count of ≥3 had approximately twice the relative risk for mortality of those that had an Elixhauser count of zero. However, adjustment for the Elixhauser instrument made no difference to

the mortality hazard ratios (HRs) for Māori women (compared with 'Other' women), and made little difference to that for Pacific women. In contrast, concurrent adjustment for 12 individual comorbid conditions from the Elixhauser instrument reduced the excess risk by 21%; and reduced the excess risk for Pacific women by 35%.

4. Travel time and distance are only weakly associated with cervical cancer screening, stage at diagnosis and mortality in New Zealand. However, travel time may explain a small amount of the ethnic differences in stage at diagnosis, and to a lesser extent mortality, particularly for Pacific women (Chapter 5). Travel time to the nearest General Practitioner (GP) was not significantly associated with late stage diagnosis, and adjustment for travel time reduced the excess risk for late-stage diagnosis by about 7% in Māori and 33% in Pacific women. Travel time to the nearest GP and cancer centre were only weakly and inconsistently associated with cervical cancer mortality (adjusted for stage), and adjustment for travel time reduced the excess risk for mortality by only 3% in Māori and 13% in Pacific women. Similar findings were observed when using travel distance rather than travel time.

5. Overall, the ethnic differences in stage at diagnosis and cervical cancer survival are only partly explained by the factors (screening history, stage at diagnosis, comorbid conditions and travel time and distance to the nearest GP and cancer centre) considered in these studies (Chapter 6). The three-fold excess risk of a late stage diagnosis in Māori women fell by only 19% when adjusted for screening history, and travel time to the nearest GP and cancer centre; in contrast, the excess risk in Pacific women fell by 85% when adjusted for these same factors. Therefore, the excess risk in Pacific women is almost entirely due to ethnic differences in screening history and travel time, whereas

the excess risk of late stage diagnosis in Māori women remains largely unexplained. Both Māori and Pacific women had about a two-fold risk of mortality from cervical cancer compared with 'Other' women, and these fell by 59% (95% confidence intervals: 29% – 88%) and 43% (95% confidence intervals: -190% – 275%) respectively when adjusted for stage at diagnosis, comorbid conditions, and travel time. Thus, about one-half of the excess risk of mortality in Māori and Pacific women is explained by differences in stage at diagnosis and comorbid conditions.

Methodological issues and limitations

The strengths and limitations of each of the studies have been discussed in depth in the respective chapters (Chapters 2-6). The major themes will be considered again here.

Ethnicity

Possible limitations of these studies include the potential for misclassification and under-counting of ethnicity. It has been estimated that there is a 17% undercount of Māori cancer registrations (Cormack *et al*, 2005) (this involves misclassification of ethnicity on registrations, rather than case under-ascertainment). Thus, the 'Other' ethnic group may contain some Māori cases that were incorrectly classified, thereby diluting the ethnic survival differences. There is also evidence of a 6-7% undercount of Māori deaths (Ajwani *et al*, 2003a; Cormack *et al*, 2005), but this would not bias these studies because the ethnicity recorded on the New Zealand Cancer Registry (NZCR) was used in all of the analyses. The classification of ethnicity was based on the wording of the corresponding census questions, and these have changed over time. However, this is unlikely to have produced serious bias because the ethnicity recorded on the NZCR

was used to classify the corresponding deaths, and the analyses were adjusted for registration year. Therefore misclassification and under-counting of ethnicity have not unduly affected the results of these studies.

Socio-economic position

There may also be misclassification of area-based SEP and urban/rural residency in the cancer registrations. However, any such misclassification is unlikely to be associated with subsequent survival and, if anything, is likely to produce underestimates of the differences in survival between these various demographic groups. Furthermore, the methods used in these studies have shown strong SEP differences for many other health problems (Haynes *et al*, 2008; McFadden *et al*, 2004; Metcalf *et al*, 2008; Robson and Harris, 2007; Tobias and Yeh, 2007); it is therefore unlikely that the methods used account for the relative lack of SEP differences found in the studies included in this thesis. SEP may have been misclassified in some instances because each woman's SEP classification was based on the area in which she lived at the time of diagnosis. Thus some women would have had higher (or lower) lifetime SEP than that of the area in which they lived (Blakely and Pearce, 2002) because they had lived in a less (or more) deprived area previously and/or because their individual SEP (as measured by income, education, *etc*) was simply different to the average SEP of the area in which they lived (Blakely and Pearce, 2002). Migration within New Zealand during the course of the disease (*i.e.* after diagnosis) can weaken the associations of cancer survival with area deprivation (Haynes *et al*, 2008). However, this issue should not be a major problem in the studies presented in this thesis because each woman was classified according to her SEP at the time of diagnosis and subsequent migration was not taken into account. It should not be concluded that women with a low SEP (as measured) had (or did not

have) poorer survival than women with a higher SEP, only that living in a deprived area at the time of diagnosis was (relatively weakly) associated with lower survival (Haynes *et al*, 2008).

Screening history

A strength of the screening history data is that a report about any cervical specimens taken in New Zealand for a screening test or for a diagnostic test, and those taken during a surgical procedure (that include a cervical component), must be sent to the National Cervical Screening Programme (NCSP) Manager for inclusion on the NCSP-Register (NCSP-R) (according to the Health (National Cervical Screening Programme) Amendment Act 2004), so for most women it is extremely unlikely that their screening histories are incomplete. However, women were able to 'opt-off' individual test results (until March 2005). There is little evidence to indicate how often this occurred, although the national 'opt off' rate in 2001 was 5.7% (Independent Monitoring Group of the National Cervical Screening Programme, 2004). From March 2005 women could not 'opt-off' individual test results but could choose to entirely withdraw from the NCSP (so that none of their test results would be held on the NCSP-R). There is no evidence of how often this occurred up to 31 December 2006 (the last date for which screening data was included in the studies presented in this thesis), but at 30 June 2009 1,346,054 women aged 20-69 years were enrolled on the NCSP-R and by 31 December 2009 47 of these women (0.003%) had withdrawn from the Programme (Smith *et al*, 2011). Similarly, it is possible that some women received cytological tests overseas prior to their diagnosis of cervical cancer within New Zealand, but the numbers are likely to be small.

The available data did not allow for the assessment of whether the smears taken within six months prior to diagnosis were due to the women being symptomatic (*i.e.* diagnostic tests) or were the women's first cytological tests taken at the appropriate time (*i.e.* screening tests). Further investigation, *e.g.* with a case notes review, would allow for these different scenarios to be distinguished.

Cervical screening guidelines are extremely complex (National Screening Unit, 2008) and the studies included in this thesis did not assess whether each individual woman had been screened according to the NCSP guidelines – rather, each case was classified according to her screening history (*e.g.* 'regular screening'), irrespective of whether this screening history was consistent with NCSP guidelines (see Chapter 3). In particular, the cases included some women who would have been too old (over 69 years) or too young (under 20 years) to have received recent or any screening (if following NCSP guidelines) prior to their diagnosis. Furthermore, it is possible that women have been categorised as 'regular screening' when actually they should have received smears more frequently than once every three years (*e.g.* if they had had a high grade abnormality) if they had been following NCSP guidelines. However, any such discrepancies would have lead to a reduction in the protective effect of regular screening found in these studies. Conversely, the methodology used in these studies did not distinguish whether a woman had been rescreened in an interval that was shorter than the standard recommended three years. Women being screened more frequently in this manner would potentially increase the protective effect of regular screening.

Thus the likely impact on the validity of the results of these studies caused by the limitations of the screening history data and classification was minimal.

Comorbidity

The comorbidity data was based on administrative in-hospital data and therefore those patients who did not attend hospital as an inpatient or day patient would not have had any conditions recorded. Some conditions may not have been recorded since coders may only include conditions that are present at the time of the cervical cancer diagnosis and affect patient management (Sarfati *et al*, 2010b). This probably results in the recording of the most active and clinically important conditions (Sarfati *et al*, 2010c), which is consistent with the finding in Chapter 4 that the associations of comorbidity with survival were slightly stronger using a one-year look-back period than when using a five-year look-back period. However, a recent study on colon cancer in New Zealand found that despite comorbid conditions being recorded more frequently in patients' medical notes than in administrative data, the use of a comorbidity measure still improved the prediction of all-cause survival in a multivariable model (Sarfati *et al*, 2010b). It is also possible that some patients had undiagnosed disease, but misclassification of this type would probably decrease the effects of comorbidity on survival (Sarfati *et al*, 2010b).

Travel time and distance

The estimates of travel time and distance are limited in their accuracy. We used domicile codes, were not able to estimate the time or distance from the patient's actual residential address, and were not able to estimate the time or distance to the actual GP surgery or cancer centre that the patient visited. Women may choose to travel to a more distant GP for a variety of reasons, but it is unlikely that they would choose to travel to a more distant cancer centre since there are only six in New Zealand. The women that choose to travel to a more distant GP are presumably more likely to live nearby to

several GPs, such that the actual time or distance travelled is not greatly different to our estimations. Thus there may be some misclassification of travel time and distance but any such misclassification is likely to be small and unlikely to have a large effect on the results of these studies.

More general limitations and strengths

An advantage of record linkage studies is their efficiency in that they involve the maximal use of existing data for epidemiological studies. However, record linkage studies have general limitations which include the reliance on data that are usually not collected specifically for research purposes, and that therefore may not include all of the pertinent variables. For example, a limitation of the studies presented in this thesis is that the NZCR and Mortality Collection do not include information on treatment or other related factors that may explain some of the survival differences found in these studies and this information therefore could not be included in the analyses. However, the lack of this information does not bias the findings presented, but rather would have been useful in assisting with the interpretation of the reasons for the observed differences.

Another general limitation of using routinely collected data is that the researcher using the data does not have control over the quality of the data collected. However, as discussed above and in Chapters 1-6, the data that I have used for the studies included in this thesis are of relatively high quality by international standards. Deterministic record linkage studies are also dependent on the accuracy of the primary key indicator which is used to identify the participants in each of the data collections used. The National Health Index (NHI) number system in New Zealand is maintained by the Ministry of

Health, and is routinely used for record linkage, including the studies presented in this thesis. It has been shown to be reliable and a recent review (Delany, 2006) concluded that "the NHI meets most of the criteria set down by international standards. The gaps that exist are relatively minor" and mainly relate to issues of encryption rather than the issues of completeness of coverage and accuracy of record linkage which are most relevant to the studies presented here.

The data collected for the studies presented in Chapters 2-6 were collected prospectively (*i.e.* they were recorded in the health systems databases at the time each event occurred) but were analysed retrospectively. This enabled survival to be investigated over a period of up to 12 years, whereas it would have taken approximately 15 years to collect such data prospectively (Ministry of Health, 2010a). On the other hand, this means that the current situation may not be the same as when the cases were diagnosed, particularly since at least some of the ethnic differences appear to have reduced over time. Nevertheless, the studies provide robust evidence for policy development and decision making.

A strength of these studies is that case under-ascertainment is unlikely (Ministry of Health, 2002) because the Cancer Registry Act came into effect in 1994 making cancer registration mandatory (Ministry of Health, 2009a). Death registration is also mandatory in New Zealand, and can be linked to cancer registrations using the NHI number and it is therefore very likely that all of the cases who died in New Zealand were identified. On the other hand, cases who died overseas would not have been identified, and this may particularly apply to Pacific cases who in some instances may have returned to the Pacific following a cervical cancer diagnosis. However, this would have produced an

under-estimation of the death rate in Pacific cases and therefore could not explain the increased risks seen in this ethnic group.

There may have been some misclassification of the cause of death, but this is likely to have been rare, since the analyses undertaken for this thesis were restricted to cases that had been registered prior to death - in such cases information from the NZCR is used to classify the underlying cause of death (New Zealand Health Information Service, 2004) meaning that misclassification of a cervical cancer death is unlikely. Furthermore, any such misclassification is unlikely to have varied significantly by ethnicity, and any resulting bias is likely to be very small (Sarfati *et al*, 2010a). The fact that only 73% of cases had an International Federation of Gynecology and Obstetrics (FIGO) code recorded could introduce selection bias, but a previous analysis found that there was little difference in overall cancer survival between those with stage data and those without stage data (Jeffreys *et al*, 2005b). It is also possible that there was residual confounding from inaccuracies in stage classification since there were not sufficient numbers to adjust for more detailed stage at diagnosis. Thus, residual confounding by stage could explain some of the results. However, the fact that the Māori/'Other' differences in survival reduced substantially when the analyses were adjusted for stage indicates that this is not likely to be a serious source of bias.

The studies presented in this thesis have used all of the information that is available through routinely collected data in New Zealand (relevant to cervical cancer). Although a number of potential limitations in the data and methodology have been identified, none of them is likely to have strongly biased the results presented in this thesis. To take this work further, different research methods would need to be employed, such as a

medical records review to obtain more detailed information about comorbid conditions and treatments.

Recommendations and future research

Improve data access

Since screening history did not fully explain the ethnic differences in stage at diagnosis, it is important that other possible explanations for these differences should be explored in further studies. These additional explanations may include delayed diagnosis, *i.e.* some women with regular screening histories may have a longer period of time between a smear that is suggestive of cancer (or the onset of symptoms) and the actual diagnosis of cancer. It is important that the screening histories of the women that develop cervical cancer are made available for researchers to examine in connection with other information, *e.g.* hospital medical records, so that issues such as time-to-diagnosis can be investigated (screening data were temporarily made available for the studies presented in this thesis, but it now appears that further screening data will not be made available by the NCSP for research that attempts to build on the findings presented in this thesis). The current independent monitoring reports of the NCSP (the only publicly available information) do not include information about waiting times for colposcopy (because the colposcopy data on the NCSP-R is incomplete) (Smith *et al*, 2011). Thus, it is impossible (with the currently available routinely collected data) to examine whether there are ethnic differences in the waiting times for colposcopy, and whether any such differences may be long enough to lead to later stages at diagnosis. The NCSP should continue its efforts to collect comprehensive information about when and how women are accessing cervical cancer related health care, and make this information

available to researchers so that compliance and monitoring of the NCSP can be undertaken to improve the Programme, and so that high quality evidence can be provided for policy development.

Increase availability of culturally appropriate health education

The reasons for delayed diagnosis and non-participation in screening are complex, but may include barriers to accessing health care (such as language, culture, income and/or education level, transportation difficulties, and the patient-doctor relationship) (Downs *et al*, 2008; McLeod *et al*, 2011). Parton (Parton, 2011) has reported that there is some evidence that suggests that, for Māori women, the barriers to accessing health care include the 'generational influence' of their parents' and whānau (wider family) experiences of health and well-being. These experiences almost subconsciously affected whether the women would seek or delay seeking health care (Parton, 2011). The women also described how their understanding of their bodies and of illness affected their health-care-seeking behaviour and attitudes (knowledge or opinions of what is normal and what should just be tolerated influenced when they would seek help). Watching family members die at a young age or suffer from a chronic illness such as diabetes mellitus made these women feel as though dying young or being sick was inevitable, and it made some of them feel scared of finding out whether something was wrong with them (so they preferred not to find out). The health education that was made available to these women, or to people that they knew, was often not culturally appropriate, and therefore was frequently underutilised and undervalued (Parton, 2011).

The intergenerational influences described in Parton's work (Parton, 2011) are not immediately amenable to change, but can be gradually addressed through societal

change leading to more education about health and well-being. However, as stated above, one of the other findings of Parton's work (Parton, 2011) was that much of the education offered in New Zealand was not presented in a manner that was culturally appropriate for Māori women. Therefore, learning more about how to adapt Pākēhā (European) models of health education to Māori culture, and implementing these findings, could help to encourage Māori women to seek health care in a more timely manner (Parton, 2011).

Continue to promote full participation in all aspects of cervical cancer screening

As well as not knowing when or how to access health information or services, Māori women may also have to contend with racism and discrimination in the health services (Ellison-Loschmann and Pearce, 2006). There is some evidence that racial discrimination is associated with poorer self-rated health in New Zealand (Harris *et al*, 2006a; Harris *et al*, 2006b), but there appears to be no evidence directly related to the cervical cancer care pathway in New Zealand. There is also some evidence (Brewer *et al*, 2007b; Brewer *et al*, 2008a; Brewer *et al*, 2008b; Coppell, 2006a; Coppell, 2006b; Independent Monitoring Group of the National Cervical Screening Programme, 2004; Smith *et al*, 2011) that histological test results for Māori and Pacific women are reported after a longer period of time than those for non-Māori, non-Pacific women, but it is unlikely that this time difference is sufficient to lead to a later stage at diagnosis since the precursor lesions are known to usually exist for several years before progressing to invasion. Failure to be invited or to return for a repeat smear after an unsatisfactory result, or to have a histological specimen taken after a high grade smear, or to experience a delay in seeing a gynaecologist, as well as not reporting symptoms, may also lead to a delay resulting in a later stage at diagnosis (Brewer *et al*, 2007b;

Brewer *et al*, 2008a; Brewer *et al*, 2008b; Coppell, 2006a; Coppell, 2006b; Independent Monitoring Group of the National Cervical Screening Programme, 2004; Ratima *et al*, 1993). The NCSP needs to increase its work to encourage women, particularly Māori and Pacific women, to attend for regular screening and to return for follow-up tests when necessary (McLeod *et al*, 2011) so that they can more fully experience the level of protection from developing cervical cancer that screening programmes afford. Smear takers and colposcopists should endeavour to run services, including providing information/education and building relationships, that are culturally appropriate (McLeod *et al*, 2011; Ratima, 1993), and to assist women to attend the services by addressing the issues described above. It is also important that high-quality data are collected and made available to researchers about attendance for follow-up tests so that a detailed examination of the women's screening histories, coupled with information on colposcopy and other diagnostic tests, can be undertaken to investigate the importance of any differences in follow-up.

Undertake further studies to gain more understanding of the role of differences in comorbid conditions and treatments received

With regard to further studies of cervical cancer survival, it is particularly important to obtain better information on comorbid conditions and treatments received. Anecdotally it is reported that Māori women are more likely than 'Other' women to miss appointments (for a variety of complex reasons) or to refuse treatment. It is imperative that national high-quality data are collected about this in order to determine whether these reports are accurate, so that, if they are, resources can be targeted towards encouraging women to attend appointments, to accept treatment (where appropriate), and to understand the importance of doing so. This work is currently being undertaken

as a further study that I have developed (this will take several years to complete and is not part of my PhD). The study is a medical records review that will supply more detailed information on comorbid conditions and treatments, and will also enable me to fill in some of the gaps in information from other sources (*e.g.* not all cases on the NZCR include stage at diagnosis). As noted above, my analyses to date have indicated that, for the earlier time period (1994-1997), both pre-diagnostic (*e.g.* screening) and post-diagnostic factors (*e.g.* treatment and comorbid conditions) contributed to the ethnic differences in survival, whereas in the later time period (2002-2005) the differences were almost entirely due to pre-diagnostic factors (*e.g.* screening). This is an unusual finding, and a major benefit of the on-going further work is that we will be able to investigate this further by linking screening data (if it is made available) with the medical-records-review data, in order to elucidate the reasons for this striking finding, and its implications for cancer-control policy. Furthermore, the corresponding analyses for Pacific cases indicated that post-diagnostic factors remain important, even in the most recent time period. The combination of the record linkage data and medical records review data will provide information on both the more historical cases and the more recent ones, and will permit a more in-depth examination of the roles of both pre-diagnostic and post-diagnostic factors.

Conclusions

In conclusion, I found that there are major ethnic differences in cervical cancer stage at diagnosis and survival in New Zealand. The excess risk of a late stage diagnosis in Pacific women is almost entirely due to differences in screening history and travel time, whereas the excess risk in Māori women remains largely unexplained. About one-half

of the excess risk of mortality in Māori and Pacific women is explained by differences in stage at diagnosis and comorbid conditions; it is possible that other factors, including possible differences in treatment and follow-up, also play a role. It appears that there are small ethnic differences at each stage of the cancer continuum (screening, diagnosis, treatment, follow-up, *etc*) and that each of these makes a small contribution to the major overall ethnic differences in survival that I have reported. The information presented in this thesis provides evidence of inequalities in cervical cancer survival and indicates areas for action to be taken to address these inequalities.

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Appendices

Appendix 1: Results for the Charlson Comorbidity Index and Elixhauser instrument (see Chapter 4) with both the one-year and the five-year look-back periods (Tables A1.1-A1.4)

Appendix 2: FIGO stage and cervical cancer survival in NZ

Appendix 3: Screening history and stage at diagnosis

Appendix 4: Comorbidity and cervical cancer survival in NZ

Appendix 5: Statement of contribution for “Travel time and distance to healthcare”

Appendix 6: Statement of contribution for “Ethnic inequalities in cervical cancer survival in NZ”

APPENDIX 1

Results for the Charlson Comorbidity Index and Elixhauser instrument (see Chapter 4) with both the one-year and the five-year look-back periods (Tables A1.1-A1.4)

Table A1.1. Characteristics of cervical cancer cases, n (%)

	Total	*One-year look-back period*								*Five-year look-back period*							
		Charlson Index				*Elixhauser comorbid conditions*				*Charlson Index*				*Elixhauser comorbid conditions*			
		0	*1*	*2*	*3+*	*0*	*1*	*2*	*3+*	*0*	*1*	*2*	*3+*	*0*	*1*	*2*	*3+*
Total	2,323 (100)	2,077 (89.4)	105 (4.5)	94 (4.1)	47 (2.0)	1,960 (84.4)	223 (9.6)	63 (2.7)	77 (3.3)	1,962 (84.5)	158 (6.8)	118 (5.1)	85 (3.7)	1,805 (77.7)	292 (12.6)	107 (4.6)	119 (5.1)
FIGO stage																	
0-IB2	1,155 (49.7)	1,101 (95.3)	30 (2.6)	17 (1.5)	7 (0.6)[a]	1,067 (92.4)	63 (5.5)	13 (1.1)	12 (1.0)[a]	1,060 (91.8)	52 (4.5)	27 (2.3)	16 (1.4)[a]	1,000 (86.6)	96 (8.3)	37 (3.2)	22 (1.9)[a]
II-IIB	262 (11.3)	228 (87.0)	9 (3.4)	21 (8.0)	4 (1.5)	207 (79.0)	32 (12.2)	11 (4.2)	12 (4.6)	208 (79.4)	18 (6.9)	24 (9.2)	12 (4.6)	182 (69.5)	46 (17.6)	14 (5.3)	20 (7.6)
III-IIIB	232 (10.0)	191 (82.3)	22 (9.5)	15 (6.5)	4 (1.7)	169 (72.8)	41 (17.7)	16 (6.9)	6 (2.6)	177 (76.3)	29 (12.5)	18 (7.8)	8 (3.5)	154 (66.4)	47 (20.3)	18 (7.8)	13 (5.6)
IVA-IVB	53 (2.3)	38 (71.7)	5 (9.4)	4 (7.6)	6 (11.3)	33 (62.3)	11 (20.8)	3 (5.7)	6 (11.3)	36 (67.9)	7 (13.2)	4 (7.6)	6 (11.3)	30 (56.6)	12 (22.6)	5 (9.4)	6 (11.3)
Missing	621 (26.7)	519 (83.6)	39 (6.3)	37 (6.0)	26 (4.2)	484 (77.9)	76 (12.2)	20 (3.2)	41 (6.6)	481 (77.5)	52 (8.4)	45 (7.3)	43 (6.9)	439 (70.7)	91 (14.7)	33 (5.3)	58 (9.3)
Ethnicity																	
Other	1,674 (72.1)	1,513 (90.4)	69 (4.1)	67 (4.0)	25 (1.5)[a]	1,444 (86.3)	141 (8.4)	41 (2.5)	48 (2.9)[a]	1,427 (85.2)	109 (6.5)	84 (5.0)	54 (3.2)[b]	1,325 (79.2)	190 (11.4)	77 (4.6)	82 (4.9)[c]
Māori	416 (17.9)	363 (87.3)	22 (5.3)	20 (4.8)	11 (2.6)	334 (80.3)	50 (12.0)	15 (3.6)	17 (4.1)	341 (82.0)	32 (7.7)	25 (6.0)	18 (4.3)	308 (74.0)	64 (15.4)	20 (4.8)	24 (5.8)
Pacific	105 (4.5)	82 (78.1)	9 (8.6)	7 (6.7)	7 (6.7)	71 (67.6)	21 (20.0)	3 (2.9)	10 (9.5)	78 (74.3)	10 (9.5)	9 (8.6)	8 (7.6)	66 (62.9)	23 (21.9)	5 (4.8)	11 (10.5)
Asian	128 (5.5)	119 (93.0)	5 (3.9)	0	4 (3.1)	111 (86.7)	11 (8.6)	4 (3.1)	2 (1.6)	116 (90.6)	7 (5.5)	0	5 (3.9)	106 (82.8)	15 (11.7)	5 (3.9)	2 (1.6)
NZDep2001, quintiles																	
1 (Least deprived)	298 (12.8)	283 (95.0)	6 (2.0)	7 (2.4)	2 (0.7)[NS]	277 (93.0)	14 (4.7)	3 (1.0)	4 (1.3)[b]	269 (90.3)	13 (4.4)	10 (3.4)	6 (2.0)[NS]	261 (87.6)	19 (6.4)	11 (3.7)	7 (2.4)[d]
2	333 (14.3)	294 (88.3)	18 (5.4)	14 (4.2)	7 (2.1)	283 (85.0)	33 (9.9)	8 (2.4)	9 (2.7)	282 (84.7)	22 (6.6)	17 (5.1)	12 (3.6)	266 (79.9)	41 (12.3)	12 (3.6)	14 (4.2)
3	416 (17.9)	369 (88.3)	22 (5.3)	14 (3.4)	11 (2.6)	350 (84.1)	37 (8.9)	12 (2.9)	17 (4.1)	349 (83.9)	30 (7.2)	17 (4.1)	20 (4.8)	325 (78.1)	43 (10.3)	21 (5.1)	27 (6.5)
4	526 (22.6)	459 (87.3)	29 (5.5)	30 (5.7)	8 (1.5)	432 (82.1)	56 (10.7)	19 (3.6)	19 (3.6)	430 (81.8)	43 (8.2)	32 (6.1)	21 (4.0)	391 (74.3)	78 (14.8)	28 (5.3)	29 (5.5)
5 (Most deprived)	623 (26.8)	559 (89.7)	22 (3.5)	24 (3.9)	18 (2.9)	510 (81.9)	67 (10.8)	21 (3.4)	25 (4.0)	525 (84.3)	41 (6.6)	34 (5.5)	23 (3.7)	463 (74.3)	92 (14.8)	31 (5.0)	37 (5.9)
Missing	127 (5.5)	113 (89.0)	8 (6.3)	5 (3.9)	1 (0.8)	108 (85.0)	16 (12.6)	0	3 (2.4)	107 (84.3)	9 (7.1)	8 (6.3)	3 (2.4)	99 (78.0)	19 (15.0)	4 (3.2)	5 (3.9)
Urban/rural residency																	
Main urban	1,640 (70.6)	1,488 (90.7)	62 (3.8)	54 (3.3)	36 (2.2)[e]	1,403 (85.6)	141 (8.6)	42 (2.6)	54 (3.3)[NS]	1,405 (85.7)	104 (6.3)	76 (4.6)	55 (3.4)[NS]	1,295 (79.0)	187 (11.4)	75 (4.6)	83 (5.1)[NS]
Secondary urban	361 (15.5)	306 (84.8)	20 (5.5)	26 (7.2)	9 (2.5)	288 (79.8)	47 (13.0)	13 (3.6)	13 (3.6)	288 (79.8)	28 (7.8)	25 (6.9)	20 (5.5)	262 (72.6)	63 (17.5)	17 (4.7)	19 (5.3)
Rural	196 (8.4)	171 (87.2)	15 (7.7)	9 (4.6)	1 (0.5)	162 (82.7)	19 (9.7)	8 (4.1)	7 (3.6)	163 (83.2)	17 (8.7)	9 (4.6)	7 (3.6)	150 (76.5)	23 (11.7)	11 (5.6)	12 (6.1)
Missing	126 (5.4)	112 (88.9)	8 (6.4)	5 (4.0)	1 (0.8)	107 (84.9)	16 (12.7)	0	3 (2.4)	106 (84.1)	9 (7.1)	8 (6.4)	3 (2.4)	98 (77.8)	19 (15.1)	4 (3.2)	5 (4.0)
Registration year																	
1994-1997	843 (36.3)	760 (90.2)	43 (5.1)	30 (3.6)	10 (1.2)[f]	714 (84.7)	82 (9.7)	24 (2.9)	23 (2.7)[NS]	727 (86.2)	56 (6.6)	42 (5.0)	18 (2.1)[NS]	668 (79.2)	110 (13.1)	34 (4.0)	31 (3.7)[NS]
1998-2001	815 (35.1)	722 (88.6)	40 (4.9)	38 (4.7)	15 (1.8)	689 (84.5)	79 (9.7)	20 (2.5)	27 (3.3)	677 (83.1)	62 (7.6)	41 (5.0)	35 (4.3)	634 (77.8)	96 (11.8)	38 (4.7)	47 (5.8)
2002-2005	665 (28.6)	595 (89.5)	22 (3.3)	26 (3.9)	22 (3.3)	557 (83.8)	62 (9.3)	19 (2.9)	27 (4.1)	558 (83.9)	40 (6.0)	35 (5.3)	32 (4.8)	503 (75.6)	86 (12.9)	35 (5.3)	41 (6.2)

FIGO: International Federation of Gynecology and Obstetrics; NZDep2001: New Zealand Deprivation Index 2001; NS: Not significant at 95%. p values from Pearson's chi-squared test. [a]p=0.0001; [b]p=0.02; [c]p=0.002; [d]p=0.006; [e]p=0.004; [f]p=0.04.

Table A1.2. Mortality by comorbidity measures

Comorbidity	*Mortality*	
	One-year look-back period	*Five-year look-back period*
	HR (95%CI)[a]	*HR (95%CI)*[a]
Death from cervical cancer		
Charlson (1 unit)	1.28 (1.14-1.44)	1.21 (1.09-1.35)
Charlson 0	1.00[b]	1.00[b]
Charlson 1	1.41 (0.93-2.13)	1.17 (0.81-1.70)
Charlson 2	1.70 (1.14-2.55)	1.58 (1.09-2.30)
Charlson 3+	3.22 (1.73-5.99)	2.06 (1.25-3.42)
Elixhauser (1 unit)	1.25 (1.11-1.40)	1.18 (1.07-1.30)
Elixhauser 0	1.00[b]	1.00[b]
Elixhauser 1	1.29 (0.96-1.75)	1.29 (0.98-1.71)
Elixhauser 2	1.33 (0.83-2.13)	1.39 (0.92-2.10)
Elixhauser 3+	2.17 (1.32-3.56)	1.66 (1.07-2.60)
Death from other causes (not cervical cancer)		
Charlson (1 unit)	1.64 (1.35-2.00)	1.69 (1.43-1.98)
Charlson 0	1.00[b]	1.00[b]
Charlson 1	1.35 (0.57-3.19)	2.65 (1.44-4.86)
Charlson 2	4.21 (2.08-8.51)	5.54 (2.85-10.78)
Charlson 3+	5.18 (1.57-17.04)	6.30 (2.71-14.65)
Elixhauser (1 unit)	1.46 (1.18-1.79)	1.64 (1.41-1.91)
Elixhauser 0	1.00[b]	1.00[b]
Elixhauser 1	2.49 (1.39-4.44)	2.51 (1.39-4.53)
Elixhauser 2	2.62 (1.20-5.72)	3.66 (1.80-7.44)
Elixhauser 3+	2.76 (1.04-7.30)	7.29 (3.71-14.29)
Total mortality		
Charlson (1 unit)	1.34 (1.21-1.48)	1.30 (1.19-1.42)
Charlson 0	1.00[b]	1.00[b]
Charlson 1	1.38 (0.95-2.01)	1.41 (1.03-1.94)
Charlson 2	2.10 (1.49-2.95)	2.01 (1.46-2.76)
Charlson 3+	3.40 (1.96-5.91)	2.49 (1.62-3.83)
Elixhauser (1 unit)	1.28 (1.15-1.41)	1.26 (1.16-1.36)
Elixhauser 0	1.00[b]	1.00[b]
Elixhauser 1	1.47 (1.13-1.92)	1.46 (1.14-1.87)
Elixhauser 2	1.48 (0.99-2.21)	1.66 (1.17-2.37)
Elixhauser 3+	2.20 (1.41-3.41)	2.23 (1.55-3.20)

HR (95% CI): Hazard ratio (95% confidence intervals). [a]Adjusted for age, registration year, stage, ethnicity, NZDep, urban/rural residency.
[b] Reference category.

Table A1.3. Elixhauser comorbid conditions frequency and cervical cancer-specific mortality adjusted for individual comorbid conditions

Comorbidity	*Frequency, n (%)*		*HR (95%CI)*[a]	
	One-year look-back period	*Five-year look-back period*	*One-year look-back period*	*Five-year look-back period*
Congestive heart failure	33 (1.4)	51 (2.2)	2.35 (1.22-4.52)	1.76 (1.01-3.08)
Cardiac arrhythmia	35 (1.5)	54 (2.3)	1.38 (0.60-3.18)	1.08 (0.54-2.13)
Valvular disease	8 (0.3)	16 (0.7)	2.84 (0.70-11.61)	1.41 (0.35-5.71)
Pulmonary circulation disorders	6 (0.3)	12 (0.5)	-	1.54 (0.38-6.27)
Peripheral vascular disorders	14 (0.6)	25 (1.1)	1.15 (0.36-3.61)	0.98 (0.36-2.67)
Hypertension uncomplicated	104 (4.5)	143 (6.2)	0.98 (0.63-1.52)	1.02 (0.69-1.51)
Hypertension complicated	4 (0.2)	5 (0.2)	1.74 (0.24-12.72)	1.74 (0.24-12.72)
Paralysis	17 (0.7)	29 (1.3)	1.26 (0.40-3.99)	0.94 (0.39-2.30)
Other neurological disorders	20 (0.9)	31 (1.3)	1.22 (0.30-4.99)	1.30 (0.47-3.55)
Chronic pulmonary disease	56 (2.4)	96 (4.1)	1.62 (0.95-2.77)	1.34 (0.85-2.11)
Diabetes uncomplicated	57 (2.5)	70 (3.0)	2.17 (1.33-3.53)	2.07 (1.32-3.27)
Diabetes complicated	15 (0.7)	21 (0.9)	10.46 (3.01-36.37)	10.46 (3.01-36.37)
Hypothyroidism	12 (0.5)	18 (0.8)	0.31 (0.07-1.27)	0.41 (0.13-1.33)
Renal failure	27 (1.2)	32 (1.4)	4.27 (2.08-8.76)	3.71 (1.83-7.50)
Liver disease	13 (0.6)	21 (0.9)	2.43 (0.76-7.78)	1.39 (0.44-4.38)
Peptic ulcer disease excluding bleeding	3 (0.1)	6 (0.3)	-	-
AIDS/HIV	0	0	-	-
Lymphoma	2 (0.1)	4 (0.2)	0.90 (0.12-6.60)	1.03 (0.25-4.24)
Solid tumour without metastasis	66 (2.8)	93 (4.0)	1.15 (0.66-1.99)	1.12 (0.70-1.81)
Rheumatoid arthritis/collagen vascular diseases	7 (0.3)	13 (0.6)	1.15 (0.42-3.16)	1.25 (0.55-2.83)
Coagulopathy	9 (0.4)	11 (0.5)	2.78 (0.68-11.43)	3.61 (1.13-11.53)
Obesity	24 (1.0)	32 (1.4)	3.52 (1.55-7.98)	3.66 (1.79-7.46)
Weight loss	7 (0.3)	10 (0.4)	0.76 (0.10-5.57)	0.35 (0.05-2.56)
Fluid and electrolyte disorders	34 (1.5)	54 (2.3)	4.03 (2.01-8.08)	4.05 (2.25-7.26)
Blood loss anaemia	36 (1.6)	38 (1.6)	2.44 (1.48-4.00)	2.44 (1.50-3.96)
Deficiency anaemia	22 (1.0)	40 (1.7)	0.57 (0.21-1.55)	0.83 (0.41-1.69)
Alcohol abuse	8 (0.3)	24 (1.0)	1.23 (0.17-8.95)	0.43 (0.10-1.82)
Drug abuse	4 (0.2)	10 (0.4)	3.28 (0.45-23.76)	4.94 (1.21-20.17)
Psychoses	7 (0.3)	21 (0.9)	0.70 (0.10-5.01)	1.51 (0.56-4.10)
Depression	9 (0.4)	28 (1.2)	1.01 (0.25-4.09)	1.43 (0.63-3.25)

HR (95% CI): Hazard ratio (95% confidence intervals). [a]Adjusted for age, registration year, stage, ethnicity, NZDep, and urban/rural residency. For the hazard ratio estimate for each comorbidity the reference group is women that do not have that comorbidity.

Table A1.4. Cervical cancer-specific mortality by ethnicity adjusted for comorbidity with one-year look-back period

Comorbidity	*Comorbidity*	*Ethnicity*			
		Other	*Māori*	*Pacific*	*Asian*
	HR (95%CI)[a]	*HR (95%CI)*[b]	*HR (95%CI)*[c]	*HR (95%CI)*[c]	*HR (95%CI)*[c]
No comorbidity adjustment/inclusion		1.00	1.56 (1.19-2.05)	1.95 (1.21-3.13)	0.72 (0.41-1.27)
Indices as continuous variable					
Charlson	1.28 (1.14-1.44)	1.00	1.57 (1.20-2.06)	1.85 (1.15-2.97)	0.73 (0.42-1.30)
Elixhauser	1.25 (1.11-1.40)	1.00	1.55 (1.19-2.04)	1.92 (1.20-3.09)	0.72 (0.41-1.26)
Individual comorbid conditions					
Congestive heart failure	2.35 (1.22-4.52)	1.00	1.57 (1.20-2.06)	1.98 (1.23-3.17)	0.72 (0.41-1.27)
Valvular disease	2.84 (0.70-11.61)	1.00	1.56 (1.19-2.04)	1.96 (1.22-3.14)	0.72 (0.41-1.27)
Hypertension, complicated	1.74 (0.24-12.72)	1.00	1.57 (1.19-2.06)	1.95 (1.22-3.13)	0.72 (0.41-1.27)
Chronic pulmonary disease	1.62 (0.95-2.77)	1.00	1.55 (1.18-2.03)	1.95 (1.22-3.13)	0.67 (0.38-1.19)
Diabetes, complicated	10.46 (3.01-36.37)	1.00	1.55 (1.18-2.04)	1.70 (1.03-2.80)	0.71 (0.40-1.25)
Renal failure	4.27 (2.08-8.76)	1.00	1.58 (1.20-2.07)	1.70 (1.04-2.77)	0.72 (0.41-1.27)
Liver disease	2.43 (0.76-7.78)	1.00	1.55 (1.18-2.03)	1.92 (1.20-3.09)	0.72 (0.41-1.26)
Coagulopathy	2.78 (0.68-11.43)	1.00	1.55 (1.18-2.03)	1.91 (1.19-3.07)	0.72 (0.41-1.27)
Obesity	3.52 (1.55-7.98)	1.00	1.55 (1.18-2.04)	1.90 (1.18-3.05)	0.72 (0.41-1.27)
Fluid and electrolyte disorders	4.03 (2.01-8.08)	1.00	1.51 (1.15-1.98)	1.97 (1.23-3.16)	0.69 (0.39-1.21)
Blood loss anaemia	2.44 (1.48-4.00)	1.00	1.53 (1.17-2.01)	1.98 (1.23-3.17)	0.71 (0.40-1.26)
Drug abuse	3.28 (0.45-23.76)	1.00	1.56 (1.19-2.04)	1.95 (1.22-3.13)	0.72 (0.41-1.27)
All 12 of the above		1.00	1.44 (1.09-1.89)	1.62 (0.98-2.68)	0.63 (0.35-1.13)

HR (95% CI): Hazard ratio (95% confidence intervals). [a]Adjusted for age, registration year, stage, ethnicity, NZDep2001 and urban/rural residency.
[b] Reference category. [c] Adjusted for age, registration year, stage, ethnicity, NZDep2001, urban/rural residency and comorbidity index.

APPENDIX 2

FIGO stage and cervical cancer survival in NZ

MASSEY UNIVERSITY
GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION TO DOCTORAL THESIS CONTAINING PUBLICATIONS

(To appear at the end of each thesis chapter/section/appendix submitted as an article/paper or collected as an appendix at the end of the thesis)

We, the candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

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Original Article

Demographic Differences in Stage at Diagnosis and Cervical Cancer Survival in New Zealand, 1994–2005

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Abstract

Objective: To investigate ethnic, socioeconomic, and urban/rural differences in stage at diagnosis and cervical cancer survival in New Zealand.
Methods: The study involved 1594 cervical cancer cases registered during 1994–2005. Cox regression was used to estimate adjusted cervical cancer mortality hazard ratios (HRs).
Results: Māori and Pacific women had higher death rates than Other (predominantly European) women, with age and year of diagnosis adjusted HRs of 2.15 (95% CI 1.68-2.75) and 1.98 (95% CI 1.25-3.13), respectively, whereas Asian women had a lower (nonstatistically significant) risk (0.81, 95% CI 0.47-1.42). Adjustment for stage reduced the HR in Māori to 1.62 (95% CI 1.25-2.09), but there was little change for Pacific or Asian women. These patterns varied over time: for cases diagnosed during 1994–1997, the HR for Māori women was 2.34 (95% CI 1.68-3.27), which reduced to 1.83 (95% CI 1.29-2.60) when adjusted for stage; for cases diagnosed during 2002–2005, the corresponding estimates were 1.54 (95% CI 0.75-3.13) and 0.90 (95% CI 0.43-1.89). Socioeconomic status and urban/rural residence had only marginal effects.
Conclusions: There were major ethnic differences in cervical cancer survival in New Zealand that were only partly explained by stage at diagnosis. These patterns varied over time, with postdiagnostic factors playing an important role in the high Māori mortality rates in the 1990s, but in more recent years, the excess mortality in Māori women appeared to be almost entirely due to stage at diagnosis, indicating that ethnic differences in access to and uptake of screening and treatment of premalignant lesions may have been playing a major role.

Introduction

In 2004, CERVICAL CANCER was the thirteenth most common site of cancer registration and death for New Zealand females,[1] and the incidence and mortality rates were moderately high compared with the rest of the developed world.[2] Over the last decade, New Zealand's rates of cervical cancer have been decreasing,[3,4] with the data for 2005 showing an age-adjusted incidence rate of 6.2 and an age-adjusted mortality rate of 1.9/100,000 women of all ages.[5] The most likely reason for these decreases is the establishment in 1991 of the New Zealand National Cervical Screening Programme (NCSP).[6] The NCSP recommends that all women aged 20–69 years have a cervical cytology test once every 3 years.[7]

There are considerable differences in cervical cancer survival between Māori and non-Māori women.[8–11] The reasons for these differences are not entirely clear, with some reports indicating that stage at diagnosis accounts for most of the survival difference, and others indicating that it explains only a small amount of the difference in relative survival rates between Māori and non-Māori/non-Pacific women.[8–11] Furthermore, corresponding analyses have not been conducted for Pacific and Asian women in New Zealand.

In the United States, socioeconomic status (SES) has been shown to be independently associated with stage at diagnosis and cervical cancer survival, and this may explain some of the ethnic differences that have been observed.[12,13] Rural residence, which can be seen as a proxy for access to care as there may be fewer primary healthcare providers as well as specialist diagnostic and treatment services, has also been shown to be associated with higher mortality rates.[13,14] However, analyses of stage at diagnosis and cause-specific cervical

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cancer survival by SES or place of residence have not been conducted in New Zealand. Furthermore, although these demographic factors are of importance in themselves, it is also of interest to determine to what extent the previously reported ethnic differences may be explained by SES or place of residence or both.

Therefore, the current study was undertaken in order to conduct a comprehensive analysis of demographic differences in stage at diagnosis and cervical cancer survival in New Zealand between 1994 and 2005.

Materials and Methods

The source population comprised all cervical cancer cases registered with the New Zealand Cancer Registry (NZCR) between January 1, 1994, and June 30, 2005. The NZCR was established in 1948, and the Cancer Registry Act came into effect in 1994, making cancer registration mandatory.[15,16] The NZCR is a member of the International Association of Cancer Registries and has satisfied the criteria for data quality for their data to be published in the *Cancer Incidence in Five Continents* series.[17–19] Pathology laboratories are the primary source of cancer data to the NZCR, and other collections (medical certificates of causes of death, coroners' findings, public hospital discharge data, and private hospital discharge returns) as well as extensive data checking are used to validate the cancer diagnoses.[20] The NZCR uses international cancer registration guidelines for assigning date of diagnosis (Susan Hanna, Team Leader, NZCR, personal communication, November 2004), and a recent study has shown 97.3% agreement within 6 weeks between the NZCR diagnosis date and clinical notes data.[21] Several studies recently demonstrated a high level of agreement in most areas of data collection between the NZCR and the other sources of information (e.g., regional databases and clinical records) used to assess the validity of the registrations and the accuracy of ethnicity data held by the NZCR.[21–23] All registrations include the National Health Index (NHI) number that uniquely identifies individual healthcare users; this was used to obtain cause-specific mortality data (from the Mortality Collection) up to the end of December 2005 (the most recent year for which data were available).

The New Zealand Central Ethics Committee reviewed the study protocol and granted ethical approval for the study.

The NZCR records self-identified ethnicity, where people may record multiple responses, based on the Statistics New Zealand Census ethnicity question (the data in the current analyses used the ethnicity definitions of the 1991, 1996, and 2001 Censuses, and there were minor differences in the wording of the questions between Censuses).[24] Participants who reported more than one ethnicity were classified into a single ethnicity using a standard system of prioritisation: Māori> Pacific>Asian>Other.[25] Participants with missing ethnicity data were included in the Other (predominantly European) ethnic group in the analyses. This approach is standard practice in New Zealand health research.[16,26]

SES was estimated using the New Zealand Deprivation Index 2001 (NZDep2001).[27] NZDep2001 is a small area composite score based on nine variables (benefit income, employment, household income, communication, transport, support, qualifications, living space, and home ownership) taken from the 2001 New Zealand Census. Each participant was assigned a score based on the residential area in which she lived (the domicile code) as recorded on the NZCR at the time of registration. These scores were then grouped into quintiles, with a value of 5 indicating that the area is in the most deprived 20% of small areas in New Zealand as measured by NZDep2001.[27]

The domicile code recorded for each participant was also used to assign urban/rural residence according to population size, based on the Statistics New Zealand classification.[28] Participants were classified as living in a main urban area (with a population of $\geq$30,000), a secondary or minor urban area (population $\geq$1,000–29,999), or a rural area (population $<$1,000).

Stage at diagnosis was obtained from the NZCR. Of the 2260 cases occurring between January 1994 and June 2005, 52% had a differentiation grade code (developed by the New Zealand Health Information Service),[20] 64% had a Surveillance, Epidemiology, and End Results (SEER) code,[29] and 74% had an International Federation of Gynecology and Obstetrics (FIGO) code.[30] Less than 1% of records contained tumor, node, metastasis (TNM) codes (the staging system developed and maintained by the American Joint Committee on Cancer). Preliminary analyses were conducted with the subgroup of 1086 patients who had both a SEER code and a FIGO code recorded, as well as the other variables being considered. These analyses yielded similar hazard ratios (HRs) by ethnicity, SES, and rural residency when adjusted for age and either FIGO or SEER code. The FIGO codes[30] were, therefore, chosen as the classification for stage at diagnosis to be used in the analyses because they were recorded in the largest number of registrations. To provide sufficient numbers in each category, the FIGO stage was grouped into four categories: 1, stages 0–IB2; 2, II–IIB; 3, III–IIIB; 4, IVA–IVB. In some analyses, the FIGO stage was also further grouped into early stage (FIGO stages 0–IB2), which corresponds to the SEER summary stage of localized only, and late stage (FIGO stages II–IVB), which corresponds to the SEER regional or invasive carcinoma stages.[29]

Women with an unknown stage at diagnosis, whose cancer was registered on the day of their death (and who were, therefore, assumed to have a death certificate-only registration), or who could not be allocated a deprivation score were excluded from the analyses. For Cox regression analyses, women were censored at the time of their death or on December 31, 2005, if they were still alive at that time.

All analyses were conducted using Intercooled Stata 8.2 for Windows (StataCorp, College Station, TX). In the preliminary analyses, logistic regression was used to determine if SES (as estimated by NZDep2001), rural residence, or ethnicity were independently associated with stage at diagnosis. The Cox proportional hazards model[31] was then used to estimate the HRs of cervical cancer death associated with ethnicity, SES, and rural residence. The models were run initially with each demographic factor being considered alone (adjusted for age and year of diagnosis as continuous variables) and then additionally adjusted for stage and, finally, also being adjusted for the other demographic variables under consideration.

Results

Between January 1994 and June 2005, 2260 cases of cervical cancer were registered on the NZCR. The following exclu-

sions were made: 17 women because their cancer registration was made on the date of the woman's death, 124 because they did not have a domicile code that could be assigned an NZDep2001 score, and 525 because they did not have a FIGO code, leaving 1594 women to be included in the analyses. Of these, 99.2% were diagnosed based on histology of the primary malignant tumor, 0.2% based on histology of metastases, 0.3% based on cytology, and 0.4% based on clinical investigation.

Twenty-three per cent (366) of the cases died from cervical cancer during the follow-up period; 74% (271) of these women were diagnosed with late stage disease. Length of follow-up ranged from 11 days to 12 years, with a mean of 5 years. A further 5% (84) of cases died from causes other than cervical cancer, and their follow-up was censored on their date of death.

Table 1 shows the characteristics of the 1594 women included in the analyses. The majority (73%) of the women were of Other (99.7% European) ethnicity, which included 2 (0.1%) women with missing ethnicity data and 3 (0.2%) women who identified as African (or cultural group of African origin). The women were aged 17–93 years (mean 48 years), with more than two thirds being diagnosed with cervical cancer before the age of 55. Most women (68%) were diagnosed at an early stage, with only 3% being diagnosed at the most advanced stage (stage IV). Twenty-eight percent lived in the most deprived NZDep2001 quintile areas in New Zealand, and 14% lived in the least deprived areas. Only 9% of the women lived in a rural area.

Table 2 shows the distribution of stage at diagnosis by ethnicity, SES, and urban/rural residence. The majority of women of all ethnicities were diagnosed with early stage (FIGO stages 0–IB2) disease. Māori women (41.4%), however, were more often diagnosed with late stage cervical cancer (FIGO stages II–IVB) compared with Pacific (32.2%), Asian (32.5%), and Other (29.7%) women. Stage at diagnosis also differed by SES, with women living in NZDep2001 quintile 1 (least deprived) being less frequently diagnosed (27.3%) at a late stage than women living in NZDep2001 quintile 5 (most deprived, 34.4%). Women living in a main (32.0%) or secondary (34.8%) urban area were more likely to have been diagnosed at a late stage than were women living in a rural area (27.9%). The differences in stage at diagnosis by ethnicity were statistically significant ($p = 0.02$), whereas those by deprivation ($p = 0.25$) and by urban/rural residence ($p = 0.71$) were not.

Logistic regression was used to examine the odds ratio (OR) of a late stage compared with an early stage at diagnosis (Table 2). Māori women (OR 2.75, 95% CI 2.04-3.70) were considerably more likely to be diagnosed at a late stage compared with Other women. Pacific women (OR 1.38, 95% CI 0.76-2.49) appeared to follow the same pattern (although the result was not statistically significant), but there was no evidence that Asian women (OR 1.05, 95% CI 0.62-1.77) were diagnosed later than Other women. Compared with women living in areas with the lowest level of deprivation, women in the highest deprivation areas were more likely to be diagnosed at a late stage (OR 1.52, 95% CI 1.03-2.25). There was little evidence that women in secondary urban areas (OR 1.09, 95% CI 0.80-1.50) or women in rural areas (OR 1.02, 95% 0.67-1.53) were more likely than women living in main urban areas to be diagnosed at a late stage. When the individual demographic variables were adjusted for each other, the ethnic differences remained largely unchanged, whereas the associations with area-based levels of deprivation largely disappeared, as did the differences between urban and rural residence.

Table 1. Characteristics of Women Diagnosed with Cervical Cancer in New Zealand, 1994 to June 2005

Characteristic	*Number*	*%*
Ethnicity		
Other	1,163	73.0
Māori	292	18.3
Pacific	59	3.7
Asian	80	5.0
Age, years		
15–24	28	1.8
25–34	304	19.1
35–44	440	27.6
45–54	335	21.0
55–64	200	12.6
65–74	175	11.0
75–84	92	5.8
≥85	20	1.3
FIGO stage		
0–IB2	1,083	67.9
II–IIB	242	15.2
III–IIIB	219	13.7
IVA–IVB	50	3.1
NZDep2001,[a] quintiles		
1 (least deprived)	220	13.8
2	233	14.6
3	304	19.1
4	386	24.2
5 (most deprived)	451	28.3
Urban/rural		
Main urban	1,194	74.9
Secondary urban	253	15.9
Rural	147	9.2
Year of diagnosis		
1994	140	8.8
1995	121	7.6
1996	149	9.4
1997	134	8.4
1998	154	9.7
1999	167	10.5
2000	174	10.9
2001	164	10.3
2002	145	9.1
2003	107	6.7
2004	103	6.5
2005 (to June 30)	36	2.3

[a]NZDep2001, New Zealand Deprivation Index 2001.

Table 3 shows the HRs for mortality by ethnicity, SES, urban/rural residence, and stage at diagnosis. Māori women had a high HR of 2.15 (95% CI 1.68-2.75), and this excess risk reduced by about one half to 1.62 (95% CI 1.25-2.09) when adjusted for stage. Further adjustment for SES and urban/rural residence produced only a small additional reduction in the HR to 1.56 (95% CI 1.19-2.05). In contrast, the high HR for Pacific women (1.98, 95% CI 1.25-3.13) remained basically unchanged when adjusted for stage (1.96, 95% CI 1.23-3.12) and when adjusted for the other demographic variables (1.95, 95% CI 1.21-3.13). Asian women had a lower HR (0.81, 95% CI 0.47-1.42), but this also did not substantially change when adjusted for stage (0.70, 95% CI 0.40-1.23) or the other demographic variables (0.72, 95% CI 0.41-1.27).

TABLE 2. STAGE AT DIAGNOSIS BY ETHNICITY, SOCIOECONOMIC STATUS, AND URBAN/RURAL RESIDENCE

	FIGO stage at diagnosis, n (%)				*Odds ratios for late stage diagnosis (stage II–IV) vs. early stage diagnosis (0–IB2)*	
	0–IB2	*II–IIB*	*III–IIIB*	*IVA–IVB*	*OR (95% CI) adjusted for age and year of diagnosis*	*OR (95% CI) adjusted for age, year of diagnosis and other variables in table*
Ethnicity						
Other	818 (70.3)	172 (14.8)	142 (12.2)	31 (2.7)	1.00[b]	1.00[b]
Māori	171 (58.6)	52 (17.8)	57 (19.5)	12 (4.1)	2.75 (2.04–3.70)	2.72 (1.98–3.73)
Pacific	40 (67.8)	9 (15.3)	7 (11.9)	3 (5.1)	1.38 (0.76–2.49)	1.38 (0.76–2.53)
Asian	54 (67.5)	9 (11.3)	13 (16.3)	4 (5.0)	1.05 (0.62–1.77)	1.07 (0.63–1.81)
NZDep2001,[a] quintiles						
1 (least deprived)	160 (72.7)	32 (14.5)	26 (11.8)	2 (0.9)	1.00[b]	1.00[b]
2	172 (73.8)	32 (13.7)	23 (9.9)	6 (2.6)	0.94 (0.60–1.49)	0.90 (0.57–1.44)
3	205 (67.4)	46 (15.1)	41 (13.5)	12 (3.9)	1.36 (0.89–2.07)	1.24 (0.81–1.91)
4	250 (64.8)	64 (16.6)	61 (15.8)	11 (2.8)	1.41 (0.95–2.11)	1.26 (0.84–1.90)
5 (most deprived)	296 (65.6)	68 (15.1)	68 (15.1)	19 (4.2)	1.52 (1.03–2.25)	1.10 (0.73–1.66)
Urban/rural residence						
Main urban	812 (68.0)	185 (15.5)	163 (13.7)	34 (2.8)	1.00[b]	1.00[b]
Secondary urban	165 (65.2)	38 (15.0)	39 (15.4)	11 (4.3)	1.09 (0.80–1.50)	0.97 (0.70–1.34)
Rural	106 (72.1)	19 (12.9)	17 (11.6)	5 (3.4)	1.02 (0.67–1.53)	0.97 (0.64–1.48)

[a]NZDep2001, New Zealand Deprivation Index 2001.
[b]Reference category.

There were also relatively strong SES differences in HRs, with women in the most deprived areas having a HR of 1.58 (95% CI 1.10-2.28) compared with those in the lowest level of deprivation. In general, these HRs changed only a small amount when adjusted for stage at diagnosis but reduced more substantially when adjusted for ethnicity and urban/rural residence. The main determinant of this reduction in the HR was ethnicity. For example, the HR for quintile 5 reduced from 1.58 (95% CI 1.10-2.28) to 1.38 (95% CI 0.95-2.00) when adjusted for stage (Table 3), then only reduced to 1.35 (95% CI 0.93-1.96) when adjusted for urban/rural residence but reduced further to 1.13 (95% CI 0.77-1.68) when adjusted for ethnicity (not shown in Table 3).

Women living in secondary urban areas had a higher HR (1.24, 95% CI 0.95-1.62) than women living in a main urban (reference category) or rural area (1.03, 95% CI 0.70-1.50), but this excess risk largely disappeared when adjusted for ethnicity and SES. The HR for secondary urban areas reduced from 1.24 (95% CI 0.95-1.62) to 1.21 (95% CI 0.93-1.59) when adjusted for stage (Table 3), then reduced to 1.19 (95% CI 0.91-1.55) when adjusted for deprivation, and reduced further to 1.14 (95% CI 0.87-1.50) when adjusted for ethnicity. For women living in a rural area, adjustment for stage increased the HR to 1.19 (95% CI 0.81-1.74), adjustment for deprivation leaving the HR unchanged at 1.19 (95% CI 0.81-1.75), and further adjustment for ethnicity reducing the HR to 1.11 (95% CI 0.75-1.64).

Table 4 shows the same analyses as in Table 3 conducted separately in those diagnosed at an early stage and those diagnosed at a late stage. In general, the demographic differences in survival were slightly stronger in cases that were diagnosed at an early stage than in those diagnosed at a late stage, but the HRs were not substantially different between the two groups of cases, and the small observed differences were not statistically significant.

As the strongest differences were observed for ethnicity, the patterns by ethnicity were investigated further to assess whether they differed by time period of cancer diagnosis. HRs for each ethnic group were calculated for three 4-year periods (1994–1997, 1998–2001, and 2002–2005) by stage at diagnosis, SES, and urban/rural residence (Table 5). The ethnic-specific HRs differed significantly by time period of diagnosis (test for interaction for the findings in column 3 of Table 5, $p < 0.01$). For cases diagnosed during 1994–1997, Māori women (compared with Other women) had an age and year of diagnosis adjusted HR of 2.34 (95% CI 1.68-3.27), which reduced to 1.83 (95% CI 1.29-2.60) when it was adjusted for stage at diagnosis and changed little when also adjusted for SES and urban/rural residence. In contrast, for cases diagnosed during 1998–2001, stage at diagnosis accounted for a larger proportion of the excess risk in Māori women: the age and year of diagnosis adjusted HR of 2.01 (95% CI 1.29-3.12) reduced to 1.25 (95% CI 0.79-1.98) when it was adjusted for stage at diagnosis and further reduced to 1.09 (95% CI 0.67-1.79) when adjusted for SES and urban/rural residence. For cases diagnosed during 2002–2005, stage at diagnosis accounted for almost all the excess relative risk (RR) in Māori women: age and year of diagnosis adjusted HR 1.54 (95% CI 0.75-3.13), age, year of diagnosis, and stage adjusted HR 0.90 (95% CI 0.43-1.89), and age, year of diagnosis, stage, SES, and urban/rural residence adjusted HR 0.82 (95% CI 0.35-1.92). In contrast, adjustment for stage at diagnosis made little difference to the HRs for

Table 3. Hazard Ratios for Mortality by Ethnicity, Socioeconomic Status, Urban/Rural Residence, and Stage at Diagnosis

	Number of deaths	*Median survival time (years)*	*HR (95% CI) adjusted for age and year of diagnosis*	*HR (95% CI) adjusted for age, year of diagnosis and stage*	*HR (95% CI) adjusted for age, year of diagnosis, stage and other variables in table*
Ethnicity					
Other	241	4.82	1.00[b]	1.00[b]	1.00[b]
Māori	92	3.98	2.15 (1.68–2.75)	1.62 (1.25–2.09)	1.56 (1.19–2.05)
Pacific	20	4.03	1.98 (1.25–3.13)	1.96 (1.23–3.12)	1.95 (1.21–3.13)
Asian	13	5.51	0.81 (0.47–1.42)	0.70 (0.40–1.23)	0.72 (0.41–1.27)
Stage at diagnosis					
0–IB2	95	5.51	1.00[b]	1.00[b]	1.00[b]
II–IIB	92	3.45	4.60 (3.40–6.21)	4.60 (3.40–6.21)	4.15 (3.06–5.63)
III–IIIB	136	1.38	11.06 (8.31–14.71)	11.06 (8.31–14.71)	10.32 (7.73–13.77)
IVA–IVB	43	0.60	25.75 (17.82–37.22)	25.75 (17.82–37.22)	23.96 (16.53–34.73)
NZDep2001,[a] quintiles					
1 (least deprived)	38	4.96	1.00[b]	1.00[b]	1.00[b]
2	41	4.67	1.00 (0.64–1.55)	1.00 (0.64–1.55)	0.95 (0.61–1.48)
3	75	4.10	1.59 (1.08–2.35)	1.38 (0.93–2.05)	1.28 (0.86–1.91)
4	95	4.73	1.43 (0.98–2.08)	1.21 (0.83–1.77)	1.11 (0.76–1.64)
5 (most deprived)	117	4.76	1.58 (1.10–2.28)	1.38 (0.95–2.00)	1.13 (0.77–1.68)
Urban/rural residence					
Main urban	268	4.61	1.00[b]	1.00[b]	1.00[b]
Secondary urban	68	4.63	1.24 (0.95–1.62)	1.21 (0.93–1.59)	1.14 (0.87–1.50)
Rural	30	5.02	1.03 (0.70–1.50)	1.19 (0.81–1.74)	1.11 (0.75–1.64)

[a]NZDep2001, New Zealand Deprivation Index 2001.
[b]Reference category.

Table 4. Hazard Ratios for Mortality by Ethnicity, Socioeconomic Status, Urban/Rural Residence, and Stage at Diagnosis[a]

	Number of deaths	*Early stage HR (95% CI)*	*Number of deaths*	*Late stage HR (95% CI)*
Ethnicity				
Other	64	1.00[c]	177	1.00[c]
Māori	20	1.73 (1.01–2.97)	72	1.46 (1.06–2.01)
Pacific	8	2.76 (1.29–5.95)	12	1.56 (0.85–2.87)
Asian	3	0.79 (0.25–2.53)	10	0.71 (0.37–1.37)
NZDep2001,[b] quintiles				
1 (least deprived)	10	1.00[c]	28	1.00[c]
2	13	1.16 (0.51–2.65)	28	0.87 (0.51–1.48)
3	17	1.27 (0.58–2.80)	58	1.22 (0.76–1.95)
4	24	1.22 (0.57–2.58)	71	1.04 (0.66–1.64)
5 (most deprived)	31	1.18 (0.56–2.48)	86	1.07 (0.67–1.70)
Urban/rural residence				
Main urban	66	1.00[c]	202	1.00[c]
Secondary urban	22	1.51 (0.91–2.48)	46	1.02 (0.73–1.42)
Rural	7	0.85 (0.39–1.87)	23	1.26 (0.79–1.98)

[a]All analyses were adjusted for age, year of diagnosis, and the other variables listed in the table. The analyses for late stage cervical cancer cases were also adjusted for stage (II, III, or IV).
[b]NZDep2001, New Zealand Deprivation Index 2001.
[c]Reference category.

Pacific and Asian women in each time period, but the numbers involved were relatively small and the CIs were correspondingly wide.

Discussion

This study found that there are major ethnic differences in cervical cancer survival in New Zealand, particularly between Māori and the Other (predominantly European) ethnic group, which are partly explained by differences in stage at diagnosis but which are not explained to any significant extent by area-based SES or urban/rural residency. In contrast, the high death rate in Pacific women's cervical cancer cases remained virtually unchanged when adjusted for stage at diagnosis, and there was a small non-significantly reduced risk in Asian cases. The socioeconomic differences in survival were only of moderate strength and largely disappeared when adjusted for ethnicity, and the urban/rural differences in survival were relatively small.

A new finding of this study is that the magnitude of the Māori/non-Māori differences and the importance of stage at diagnosis as an explanation for the higher death rate in Māori

Table 5. Hazard Ratios for Mortality by Ethnicity, Stage at Diagnosis, Socioeconomic Status, Urban/Rural Residence, and Time Period

	Number of deaths	*HR (95% CI) adjusted for age and year of diagnosis*	*HR (95% CI) adjusted for age, year of diagnosis and stage*	*HR (95% CI) adjusted for age, year of diagnosis, stage and other variables*[a]
1994–1997				
Ethnicity				
Other	111	1.00[b]	1.00[b]	1.00[b]
Māori	54	2.34 (1.68–3.27)	1.83 (1.29–2.60)	1.90 (1.29–2.79)
Pacific	9	1.51 (0.76–2.98)	1.50 (0.74–3.01)	1.76 (0.85–3.64)
Asian	2	0.29 (0.07–1.17)	0.23 (0.06–0.95)	0.25 (0.06–1.02)
1998–2001				
Ethnicity				
Other	96	1.00[b]	1.00[b]	1.00[b]
Māori	28	2.01 (1.29–3.12)	1.25 (0.79–1.98)	1.09 (0.67–1.79)
Pacific	5	1.85 (0.75–4.56)	1.78 (0.72–4.40)	1.37 (0.53–3.50)
Asian	9	1.57 (0.79–3.12)	1.39 (0.70–2.76)	1.28 (0.64–2.56)
2002–2005				
Ethnicity				
Other	34	1.00[b]	1.00[b]	1.00[b]
Māori	10	1.54 (0.75–3.13)	0.90 (0.43–1.89)	0.82 (0.35–1.92)
Pacific	6	3.49 (1.45–8.42)	5.56 (2.22–13.94)	5.15 (1.89–14.03)
Asian	2	0.61 (0.15–2.57)	0.56 (0.13–2.38)	0.77 (0.18–3.37)

[a]Other variables were socioeconomic status and urban/rural residence.
[b]Reference category.

women have changed over time (Table 5). These findings are largely consistent with evidence that (1) Māori/non-Māori inequalities in life expectancy widened during the 1990s, when general socioeconomic inequalities in New Zealand increased, and that widening inequalities in cancer mortality accounted for a substantial proportion of this trend,[32] and (2) the Māori/non-Māori differences began to stabilize or even decrease in the late 1990s.[33] With regard to the specific findings for cervical cancer mortality reported here, in the earliest time period investigated (1994–1997), about one half of the excess mortality in Māori women was due to stage at diagnosis, but one-half was not, indicating that both prediagnostic and postdiagnostic factors were playing an important role. By the latest time period examined (2002–2005), the Māori excess mortality had decreased, and stage at diagnosis accounted for all the remaining excess mortality risk in Māori women, indicating that in more recent times, prediagnostic factors have become relatively more important. These prediagnostic factors may include differences in screening rates and also in the timeliness of follow-up and subsequent treatment (of premalignant changes) of women with an abnormal cervical cytology result.[4] In Pacific women, however, stage at diagnosis was associated with only a small amount of the survival differences in each time period, a finding that is consistent with the stage distribution (Table 2) in Pacific women not being very different to that in Other women. The excess risk in Pacific women is, therefore, not due to stage at diagnosis but is likely to be due to postdiagnosis factors, such as access to and uptake of treatment.

Internationally, ethnicity has been shown consistently to be a risk factor for late stage cervical cancer diagnosis,[12,34] and in New Zealand, it has been shown that Māori women are more likely than non-Māori women to be diagnosed with cervical cancer at a late stage.[11,35] The results of the current study confirm these findings, suggesting that Māori women are more likely to be diagnosed at a late stage, independent of SES and urban/rural residence. Similar findings have been reported for other cancers.[36,37]

Although there have been no previously published New Zealand studies of the effect of urban/rural residence on cervical cancer survival, studies on survival of cancer of the colorectum and anus, trachea, bronchus and lung, breast, prostate, melanoma,[37] upper gastrointestine,[38] and breast[39] in New Zealand have shown that geographic location has only a small effect on survival. SES, as estimated by an area-based composite score (NZDep2001), gave only moderately strong findings, which decreased slightly with adjustment for stage at diagnosis but decreased substantially when adjusted for ethnicity and urban/rural residence. As noted, most of this change was due to the adjustment for ethnicity. Conversely, as the findings by ethnicity hardly changed when they were adjusted for SES and urban/rural residence, ethnicity was not confounded by SES.

What could explain these findings? They are very unlikely to be due to biological or genetic differences[40] because these generally only have a very weak association with ethnicity,[41] a concept that incorporates biology but also includes a wide variety of historical, cultural, and lifestyle factors.[42] It is well established that there are major ethnic differences in access to and uptake of cervical cancer screening in New Zealand.[4] These appear to account for about one half of the increased mortality in Māori cervical cancer cases in the 1990s but almost all the Māori excess mortality in the more recent time period (2002–2005), although other prediagnostic factors may also play a role. The rest of the excess Māori mortality during the 1990s and virtually all of the excess Pacific mortality throughout the entire time period (1994–2005) appear to be due to postdiagnostic factors. One obvious possibility is the previously documented ethnic differences in access to healthcare in New Zealand.[43–45] Studies in the United States have found that the quality of cancer treatment differs by ethnicity,[46] and it is possible that this is also the case in New Zealand (although the authors are not aware of any specific studies of this in New Zealand). It should be noted that higher comorbidities in Māori and Pacific women could also limit treatment and posttreatment options,[10] but it is currently unclear what proportion of the ethnic differences is accounted for by such comorbidities.

The strengths and limitations of this study should be acknowledged. A strength of the study is that the Cancer Registry Act came into effect in 1994, making cancer registration mandatory,[15] and case underascertainment is, therefore, unlikely.[16] Death registration is also mandatory in New Zealand and can be linked to cancer registrations using the NHI number; thus, it is very likely that all the patients who died in New Zealand were identified. On the other hand, cases that died overseas would not have been identified, and this may particularly apply to Pacific patients, who in some instances may have returned to the Pacific following a cervical cancer diagnosis. However, this would have produced an underestimation of the death rate in Pacific women and, therefore, could not explain the increased risks seen in this ethnic group.

There may have been some misclassification of cause of death, but this is unlikely to have been major or to have varied significantly by ethnicity because the analyses were restricted to cases that had been registered prior to death. Furthermore, in cases that are registered prior to death, information from the NZCR is used to classify the underlying cause of death[20]; misclassification of a cervical cancer death is, therefore, unlikely. The fact that only 73% of cases had a FIGO code recorded could introduce selection bias, but a previous analysis found that there was little difference in overall cancer survival between those with stage data and those without stage data.[10] It is also possible that there was residual confounding from inaccuracies in stage classification, as there were not sufficient numbers to adjust for more detailed stage at diagnosis. Thus, residual confounding by stage could explain some of the results. However, the fact that the Māori/Other differences almost completely disappeared when the analyses were adjusted for stage indicates that this is not likely to be a serious source of bias.

Other possible limitations of the study include the potential misclassification of ethnicity, which has been estimated as a 17% undercount of Māori cancer registrations[44] (this involves misclassification on ethnicity on registrations rather than case underascertainment). Thus, the Other ethnic group may contain some Māori cases that were incorrectly classified, thereby diluting the ethnic survival differences. As noted, the classification of ethnicity was based on the wording of the corresponding Census questions, and these have changed over time; once again, however, this is unlikely to have produced serious bias because the ethnicity recorded on the NZCR was also used to classify the corresponding deaths, and the analyses were adjusted for year of diagnosis.

There may also be misclassification of area-based SES and urban/rural residency in cancer registrations, but in each instance, any such misclassification is unlikely to be associated with subsequent survival and, if anything, is likely to produce underestimates of the differences in survival between these various demographic groups. Furthermore, the methods used in this study are standard and have shown strong SES differences for many other health problems.[11,37,45,47,48] It is, therefore, unlikely that the methods used account for the relative lack of SES differences found in the current study. The final limitation of the study is that the NZCR and Mortality Collection do not include information on comorbidities, treatment, or other related factors that may explain some of the survival differences found in this study, and this information, therefore, could not be included in the analyses. However, the lack of this information does not represent a bias in the findings presented but rather would have been useful in terms of interpreting the reasons for the observed differences.

These initial analyses of inequalities in cervical cancer survival in New Zealand provide timely baseline data. New Zealand commenced a vaccination program with Gardasil (Merck, Auckland, NZ) in September 2008, which will provide vaccinated women with immunity to human papillomavirus (HPV) subtypes 16, 18, 6, and 11. However, subtypes 16 and 18 are estimated to account for only about 70% of current cervical cancer cases (the exact figure is unknown because a national HPV prevalence survey has not been done). Furthermore, the vaccine will not yield major benefits for several decades, and the duration of protection provided by the vaccine is currently unknown. It is as yet not known what the uptake of the vaccine will be across various demographic groups and, thus, whether, for example, it will increase or decrease the relative inequalities by ethnicity in cervical cancer incidence, mortality, and survival.

Conclusions

This study has found that there are major ethnic differences in cervical cancer survival, which are in part explained by differences in stage at diagnosis. After adjustment for stage at diagnosis, Māori ethnicity was still a major determinant of cervical cancer survival in 1994–1997 but not in later years. Survival was worse for Pacific cases for all three time periods, but the numbers were relatively small. SES and urban/rural residence had only relatively weak independent associations with survival. Thus, for the earlier time period (1994–1997), both prediagnostic and postdiagnostic factors contributed to the Māori/Other differences in survival, whereas in the later time period (2002–2005), the differences were almost entirely due to prediagnostic factors. In contrast, the corresponding analyses for Pacific cases indicated that postdiagnostic factors remain important, even in the most recent time period. These findings of past differences warrant further investigation, including consideration of data on screening history, comorbidities, and access to cancer treatment.

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Disclosure Statement

The authors have no conflicts of interest to report.

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APPENDIX 3

Screening history and stage at diagnosis

MASSEY UNIVERSITY
GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION TO DOCTORAL THESIS CONTAINING PUBLICATIONS

(To appear at the end of each thesis chapter/section/appendix submitted as an article/paper or collected as an appendix at the end of the thesis)

We, the candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of Candidate: NAOMI BREWER

Name/Title of Principal Supervisor: ASSOCIATE PROFESSOR BARRY BORMAN

Name of Published Research Output and full reference: Does screening history explain the ethnic differences in stage at diagnosis of cervical cancer in New Zealand? International Journal of Epidemiology 2010;39(1): 156-165

In which Chapter is the Published Work: CHAPTER THREE

Please indicate either:

- **The percentage of the Published Work that was contributed by the candidate:** 85%
  and / or
- **Describe the contribution that the candidate has made to the Published Work:**

N Brewer
Candidate's Signature

2/11/11
Date

Principal Supervisor's signature

2/11/11
Date

Brewer N, Pearce N, Jeffreys M, Borman B, Ellison-Loschmann L. Does screening history explain the ethnic differences in stage at diagnosis of cervical cancer in New Zealand? *International Journal of Epidemiology* 2010; 39 (1): 156-165, by permission of the International Epidemiological Association.

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CANCER

Does screening history explain the ethnic differences in stage at diagnosis of cervical cancer in New Zealand?

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Background There are ethnic disparities in cervical cancer survival in New Zealand. The objectives of this study were to assess the associations of screening history, ethnicity, socio-economic status (SES) and rural residence with stage at diagnosis in women diagnosed with cervical cancer in New Zealand during 1994–2005.

Methods The 2323 cases were categorized as 'ever screened' if they had had at least one smear prior to 6 months before diagnosis, and as 'regular screening' if they had had no more than 36 months between any two smears in the period 6–114 months before diagnosis. Logistic regression was used to estimate the associations of screening history, ethnicity, SES and urban/rural residence with stage at diagnosis.

Results The percentages 'ever screened' were 43.3% overall, 24.8% in Pacific, 30.5% in Asian, 40.6% in Māori and 46.1% in 'Other' women. The corresponding estimates for 'regular screening' were 14.0, 5.7, 7.8, 12.5 and 15.3%. Women with 'regular screening' had a lower risk of late stage diagnosis [odds ratio (OR) 0.16, 95% confidence interval (CI) 0.10–0.26], and the effect was greater for squamous cell carcinoma (OR 0.12, 95% CI 0.07–0.23) than for adenocarcinoma (OR 0.32, 95% CI 0.13–0.82). The increased risk of late-stage diagnosis (OR 2.72, 95% CI 1.99–3.72) in Māori (compared with 'Other') women decreased only slightly when adjusted for screening history (OR 2.45, 95% CI 1.77–3.39).

Conclusions Over half of cases had not been 'ever screened'. Regular screening substantially lowered the risk of being diagnosed at a late stage. However, screening history does not appear to explain the ethnic differences in stage at diagnosis.

Keywords New Zealand, screening, uterine cervical neoplasms

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Introduction

In 2005, cervical cancer was the ninth most common site of cancer registration for New Zealand females,[1] and the incidence and mortality rates were moderately high compared with the rest of the developed world.[2] Over the past decade, New Zealand's rates of cervical cancer have been decreasing,[3,4] with the data

for the year 2005 showing an age-adjusted incidence rate of 6.2 and an age-adjusted mortality rate of 1.9 per 100 000 women of all ages.[1] The most likely reason for these decreases is the establishment in 1990–91 of the New Zealand National Cervical Screening Programme (NCSP).[5] The NCSP recommends that all women aged 20–69 years have a cervical cytology test once every 3 years.[6]

However, incidence and mortality rates are not the same across ethnic groups within New Zealand. For example, in 2005, Māori women had an incidence rate of 9.0, Pacific women 16.3 and 'Other' (predominantly European) women 5.6 per 100 000 women; Māori women had a mortality rate of 6.5, Pacific women 7.1 and 'Other' women 1.4 per 100 000 women.[1] The current authors have previously reported demographic differences in cervical cancer survival in New Zealand.[7] Māori and Pacific women had higher death rates than 'Other' women, whereas Asian women had a lower risk. Adjustment for stage at diagnosis explained some of the increased risk in Māori women (compared with 'Other' women), but only very little of the differences in Pacific or Asian women. Socio-economic status (SES) and urban/rural residence had only marginal effects.

One possible explanation for these differences is that rates of cervical screening also differ across the ethnic groups in New Zealand. In 2006, the coverage [had a cytology or histology result recorded on the NCSP-Register (NCSP-R) in the previous 3 years] rates were 46.6% for Māori women, 43.9% for Pacific women and 75.7% for 'Other' women.[4] As part of the ongoing work to monitor and improve the NCSP, an audit of the screening histories of women diagnosed with invasive cervical cancer between 1 January 2000 and 30 September 2002 was undertaken.[8] The aims of the audit included providing information to contribute to the elimination of the ethnic disparities in the incidence of and mortality from invasive cervical cancer. The audit found that only 50% of the women had had a smear in the 6–42 months prior to diagnosis (a 3-year period) and that only 20% of the women had an adequate screening history (no interval of >3 years between screening smears in the 6 months to 7 years prior to diagnosis). The audit also found that more Māori than non-Māori women had late-stage disease [International Federation of Gynecology and Obstetrics (FIGO)[9] stage 2+] at diagnosis and that 'there was an impression that at all steps of the screening pathway, Māori women were less well served [than non-Māori women]'.[8]

The current study therefore investigated the screening history of women diagnosed with cervical cancer in New Zealand during 1994–2005, to examine the associations of screening history with stage at diagnosis, and whether differences in screening history explain the ethnic, socio-economic and urban/rural differences in stage at diagnosis.

Methods

The source population comprised all cervical cancer cases registered with the New Zealand Cancer Registry (NZCR) between 1 January 1994 and 31 December 2005. The NZCR records self-identified ethnicity, where people may record multiple responses. Participants who reported more than one ethnicity were classified into a single ethnicity using a standard system of prioritization: Māori > Pacific > Asian > 'Other'.[10] Participants with missing ethnicity data were included in the 'Other' (predominantly European) ethnic group in the analyses. This approach is standard practice in New Zealand health research.[11,12]

SES was estimated using the New Zealand Deprivation Index 2001 (NZDep2001).[13] Each participant was assigned a score based upon the residential area (the domicile code) in which they lived as recorded on the NZCR at the time of registration. These scores were then grouped into quintiles, with a value of five indicating that the area is in the most deprived 20% of small areas in New Zealand.[13]

The domicile code recorded for each participant was also used to assign urban/rural residence according to population size.[14] Participants were classified as living in a main urban area (with a population of 30 000 or more), a secondary or minor urban area (population 1000–29 999) or a rural area (population less than 1000).

The FIGO[9] stage at diagnosis was obtained from the NZCR. FIGO codes were used in these analyses because they were available for a greater number of registrations (74%) than the other staging systems recorded on the NZCR.[7] There was little ethnic difference in the percentage of cases with missing FIGO codes: 24% of Māori, 32% of Pacific, 33% of Asian and 26% of 'Other' cases had missing FIGO codes. Similarly, the percentages of cases with missing FIGO codes in each of the five quintiles of NZDep2001 were as follows: 25, 28, 26, 26 and 26%.

The FIGO stages were grouped into early stage (FIGO stages 0–IB2), which corresponds to the SEER summary stage of localized only, and late stage (FIGO stages II–IVB), which corresponds to the SEER regional or invasive carcinoma stages.[15] Women with an unknown stage at diagnosis, or who could not be allocated a deprivation score, were excluded from the analyses.

Each cervical cancer case was categorized by histological type according to the International Classification of Diseases for Oncology (ICD-O)[16] code assigned by the NZCR, as follows: adenocarcinoma (ICD-O codes 8140–8550), adenosquamous cell carcinoma (ICD-O codes 8560, 8570), squamous cell carcinoma (ICD-O codes 8050–8082), other histological types (ICD-O codes 8800–8932, 8990–8991, 9040–9044, 9120–9134 and 9540–9581) and cervical cancer not otherwise specified (NOS; ICD-O codes 8000–8004, 8010–8034, 9990).[16–18]

The National Health Index number (which uniquely identifies individual health care users) for each of the cervical cancer cases registered with the NZCR between 1994 and 2005 was used to obtain the woman's screening history from the NCSP-R. The NCSP-R is governed by the Health (National Cervical Screening Programme) Amendment Act, which came into effect in 2004, and stipulates that all cervical cytological and histological test results must be sent to the NCSP (for entry onto the NCSP-R), unless the woman chooses to withdraw her enrolment from the programme. The NCSP-R also holds basic demographic details about all enrolled women.

The classifications of screening history were based on those used for the New Zealand Cervical Cancer audit[8] and for quality monitoring by the NCSP.[19] Women were categorized as 'not screened' or 'ever screened'. The former category included: 'no screening' (no cervical smears before diagnosis); and 'pre-diagnostic only' (one or more smears in the 6 months prior to diagnosis but not previously). The latter category included: 'irregular screening—participation' (one or more smears in the period 6–84 months before diagnosis); 'irregular screening—coverage' (one or more smears in the period 6–42 months before diagnosis); 'regular screening' (meeting the criteria for 'coverage' and with no more than 36 months between any two smears in the period 6–114 months before diagnosis); and, 'screened' (one or more smears prior to 6 months before diagnosis), which described women that did not meet the criteria for the previous categories. Thus all women were categorized as either 'not screened' or 'ever screened', and then further sub-categorized into the aforementioned mutually exclusive categories. In New Zealand, women are recommended to have a screening smear once every 3 years (36 months),[6] meaning that the period of time encompassed by the 'irregular screening—participation' category should include at least two smears, and the period of time for the 'irregular screening—coverage' category should include a previous smear from a woman who had screen detected cancer (where her 'diagnostic' smear was taken in the 6 months prior to diagnosis). The final category of 'regular screening' indicates that the woman did not have an interval between smears of more than the recommended 3 years at any time in the 9 years prior to the 6 months before diagnosis. This time period allows for three screening cycles to have taken place. We excluded all of the smears taken in the 6 months immediately prior to diagnosis since some of these will have been taken for diagnostic, not screening, purposes.[20,21] Cervical screening guidelines are extremely complex,[6] and the categories used in this study are therefore only able to approximate the women's screening histories.[8]

The New Zealand Central Ethics Committee granted ethical approval for the study.

All analyses were conducted using Intercooled Stata 10 for Windows (StataCorp, College Station, TX, USA). Logistic regression was used to estimate whether the associations of screening history, ethnicity, SES or rural residence were independently associated with stage at diagnosis.

Results

There were 2323 cases of cervical cancer registered on the NZCR between 1 January 1994 and 31 December 2005, and all of these cases were included in the descriptive analyses of screening history (Table 1). Overall, more than half (56.7%) of the women had not had a screening smear. The percentages 'ever screened' and for 'regular screening' were highest in 'Other' women (46.1 and 15.3%, respectively), and lowest in Pacific women (24.8 and 5.7%, respectively). The percentages 'ever screened' also varied by age, peaking at 71.7% in women aged 25–34 years and then gradually decreasing to the lowest percentage (9.0%) in women aged $\geqslant$75 years. The percentage 'ever screened' was particularly low in women with squamous cell carcinoma (41.3%) or adenosquamous cell carcinoma (36.8%), compared with cases of adenocarcinoma (59.7%).

Screening rates increased over time (Table 1), with 29.5% of cases registered during 1994–97 (i.e. during the early years of the screening programme) having been 'ever screened', 49.8% during 1998–2001 and 52.6% during 2002–05.

In the analyses of risk factors for late-stage diagnosis (Tables 2 and 3), 621 women were excluded because they did not have a FIGO code. As noted above, these women had a similar ethnic and SES distribution to the cases that did have a FIGO code. A further 77 cases were excluded because they did not have a domicile code that could be assigned an NZDep2001 score, leaving 1625 women included in the analyses.

Table 2 shows the associations of screening history with stage at diagnosis by histological type. Compared with 'no screening smears', women with 'regular screening' had a lower risk of late-stage diagnosis [compared with early stage diagnosis; odds ratio (OR) 0.16, 95% confidence interval (CI) 0.10–0.26], and the effect appeared larger for squamous cell carcinoma (OR 0.12, 95% CI 0.07–0.23) than for adenocarcinoma (OR 0.32, 95% CI 0.13–0.82). Women who were in the categories 'irregular screening—coverage' (OR 0.19, 95% CI 0.13–0.29) and 'irregular screening—participation' (OR 0.17, 95% CI 0.10–0.31), also had lower ORs (compared with women with 'no screening smears'), but women in the 'screened' category did not (OR 0.81, 95% CI 0.39–1.69). The decreased ORs in screened women were seen in all time periods (not shown in Table 2): for example, the ORs for 'regular screening' were 0.28 (95% CI

Table 1 Characteristics of women diagnosed with cervical cancer in New Zealand, 1994–2005

Characteristic	Not screened				Ever screened											
	No smears or only after diagnosis		Smear only in 6 months prior to diagnosis		Screened		Irregular screening—participation		Irregular screening—coverage		Regular screening		Total 'ever screened'		Total participants	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Total	511	22.0	807	34.7	57	2.5	198	8.5	426	18.3	324	14.0	1005	43.3	2323	100
Ethnicity																
Other	354	21.1	549	32.8	33	2.0	149	8.9	333	19.9	256	15.3	771	46.1	1674	100
Māori	89	21.4	158	38.0	18	4.3	36	8.7	63	15.1	52	12.5	169	40.6	416	100
Pacific	42	40.0	37	35.2	5	4.8	5	4.8	10	9.5	6	5.7	26	24.8	105	100
Asian	26	20.3	63	49.2	1	0.8	8	6.3	20	15.6	10	7.8	39	30.5	128	100
Age (years)																
15–24	4	11.4	8	22.9	0	0.0	3	8.6	12	34.3	8	22.9	23	65.7	35	100
25–34	28	7.0	85	21.3	14	3.5	73	18.3	106	26.6	93	23.3	286	71.7	399	100
35–44	68	11.1	207	33.8	18	2.9	59	9.6	150	24.5	110	18.0	337	55.1	612	100
45–54	110	22.9	191	39.8	9	1.9	34	7.1	81	16.9	55	11.5	179	37.3	480	100
55–64	72	23.8	126	41.7	6	2.0	14	4.6	46	15.2	38	12.6	104	34.4	302	100
65–74	94	34.6	122	44.9	4	1.5	10	3.7	23	8.5	19	7.0	56	20.6	272	100
⩾75	135	60.5	68	30.5	6	2.7	5	2.2	8	3.6	1	0.4	20	9.0	223	100
FIGO stages																
0–IB2	118	10.2	396	34.3	22	1.9	131	11.3	280	24.2	208	18.0	641	55.5	1155	100
II–IIB	66	25.2	124	47.3	12	4.6	11	4.2	28	10.7	21	8.0	72	27.5	262	100
III–IIIB	112	48.3	76	32.8	6	2.6	11	4.7	19	8.2	8	3.4	44	19.0	232	100
IVA–IVB	26	49.1	19	35.8	2	3.8	0	0.0	4	7.5	2	3.8	8	15.1	53	100
Missing	189	30.4	192	30.9	15	2.4	45	7.2	95	15.3	85	13.7	240	38.6	621	100
Histological type																
Squamous cell carcinoma	338	19.8	663	38.9	43	2.5	153	9.0	291	17.1	217	12.7	704	41.3	1705	100
Adenosquamous carcinoma	31	24.8	48	38.4	3	2.4	10	8.0	14	11.2	19	15.2	46	36.8	125	100
Adenocarcinoma	69	18.9	78	21.4	9	2.5	26	7.1	107	29.3	76	20.8	218	59.7	365	100
Other	5	20.8	6	25.0	1	4.2	4	16.7	3	12.5	5	20.8	13	54.2	24	100
Not otherwise specified	68	65.4	12	11.5	1	1.0	5	4.8	11	10.6	7	6.7	24	23.1	104	100
NZDep2001, quintiles																
1 (least deprived)	57	19.1	98	32.9	7	2.3	33	11.1	57	19.1	46	15.4	143	48.0	298	100
2	66	19.8	115	34.5	1	0.3	24	7.2	76	22.8	51	15.3	152	45.6	333	100
3	100	24.0	125	30.0	13	3.1	30	7.2	83	20.0	65	15.6	191	45.9	416	100
4	119	22.6	201	38.2	15	2.9	46	8.7	87	16.5	58	11.0	206	39.2	526	100
5 (most deprived)	138	22.2	211	33.9	20	3.2	56	9.0	107	17.2	91	14.6	274	44.0	623	100
Missing	31	24.4	57	44.9	1	0.8	9	7.1	16	12.6	13	10.2	39	30.7	127	100

(continued)

Table 1 Continued

Characteristic	Not screened				Ever screened								Total participants	
	No smears or only after diagnosis		Smear only in 6 months prior to diagnosis		Screened		Irregular screening—participation		Irregular screening—coverage		Regular screening		Total 'ever screened'			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Urban/rural																
Main urban	362	22.1	559	34.1	45	2.7	140	8.5	300	18.3	234	14.3	719	43.8	1640	100
Secondary urban	79	21.9	134	37.1	7	1.9	31	8.6	65	18.0	45	12.5	148	41.0	361	100
Rural	39	19.9	58	29.6	4	2.0	18	9.2	45	23.0	32	16.3	99	50.5	196	100
Missing	31	24.6	56	44.4	1	0.8	9	7.1	16	12.7	13	10.3	39	31.0	126	100
Year of diagnosis																
1994–97	220	26.1	374	44.4	0	0.0	23	2.7	121	14.4	105	12.5	249	29.5	843	100
1998–2001	156	19.1	253	31.0	18	2.2	83	10.2	161	19.8	144	17.7	406	49.8	815	100
2002–05	135	20.3	180	27.1	39	5.9	92	13.8	144	21.7	75	11.3	350	52.6	665	100
Screened in 6 months prior																
Yes	0	0.0	807	49.1	42	2.6	176	10.7	349	21.2	270	16.4	837	50.9	1644	100
No	511	75.3	0	0.0	15	2.2	22	3.2	77	11.3	54	8.0	168	24.7	679	100

FIGO: International Federation of Gynecology and Obstetrics; NZDep 2001: New Zealand Deprivation Index 2001.

0.12-0.68) in 1994–97, 0.13 (95% CI 0.06–0.26) in 1998–2001 and 0.06 (95% CI 0.01–0.21) in 2002–05.

Table 3 shows the associations of ethnicity, SES and urban/rural residence with stage at diagnosis. In general, adjustment for screening history made little difference to the demographic differences in stage at diagnosis. In particular, the increased risk of a late-stage diagnosis for Māori women decreased only slightly (from 2.72 to 2.45) when adjusted for screening history. In contrast, the increased risk for a late stage diagnosis for Pacific women (OR 1.45) disappeared when adjusted for screening history (OR 0.99). These findings were maintained when the analysis was repeated for the subgroup of women with squamous cell carcinoma (Table 3). However, there were quite different patterns for adenocarcinoma, with Māori, Pacific and Asian women showing increased risks of a late stage of diagnosis, which decreased only slightly when adjusted for screening history.

Discussion

The general strengths and limitations of the data on which these new analyses are based have been described previously,[7] and we will therefore focus on factors related to the new findings that have been presented here, i.e. the screening histories. One of the strengths of the screening history data is that all cervical smear results taken within New Zealand are required by law to be sent to the NCSP-R, and so for most women it is extremely unlikely that their screening histories are incomplete. However, women were able to 'opt-off' individual test results, and it is not clear how often this occurred, although the national rate in 2001 was 5.7%.[22] Similarly, it is possible that some women received cytological tests overseas prior to their diagnosis of cervical cancer within New Zealand, but the numbers are likely to be small.

The available data did not allow for the assessment of whether the smears taken within 6 months prior to diagnosis were due to the women being symptomatic (i.e. diagnostic tests) or were the women's first cytological tests taken at the appropriate time (i.e. screening tests). Further investigation, for example, with a case notes review, would allow for these different scenarios to be distinguished.

A further limitation of the study was that 26% of cases were missing a FIGO code. However, this is unlikely to have biased the findings, particularly the comparisons between Māori and 'Other' women because the proportions missing FIGO codes were very similar (24 and 26%, respectively), and the lowest proportion with missing FIGO stage was actually in Māori women.

We used an area-based measure of SES,[13] and it is possible that some individual cases were therefore misclassified. However, the measure used is standard and has shown strong SES differences for many other

Table 2 Odds ratios (95% CI) for screening history and late-stage diagnosis (stages II–IV) versus early-stage diagnosis (stages 0–IB2)[a]

	Histological type		
Screening history	All cases	Squamous cell carcinoma	Adenocarcinoma[b]
No screening smears	1.00[c]	1.00[c]	1.00[c]
'Diagnostic' only	0.39 (0.28–0.53)	0.39 (0.28–0.56)	0.29 (0.13–0.66)
Screened	0.81 (0.39–1.69)	0.78 (0.34–1.77)	1.46 (0.27–7.96)
Irregular participation	0.17 (0.10–0.31)	0.16 (0.08–0.30)	0.28 (0.07–1.14)
Irregular coverage	0.19 (0.13–0.29)	0.17 (0.10–0.28)	0.34 (0.14–0.84)
Regular	0.16 (0.10–0.26)	0.12 (0.07–0.23)	0.32 (0.13–0.82)

[a]Adjusted for age, registration year, ethnicity, NZDep2001, urban/rural residence.
[b]Adenocarcinoma including adenosquamous carcinoma.
[c]Reference category.

health problems;[23–27] furthermore, information on other possible measures of SES (e.g. income, education, occupation) were not available.

Cervical screening guidelines are extremely complex[6] and the current study did not assess whether each individual woman had been screened according to the NCSP guidelines—rather, we classified each case according to her screening history (e.g. 'regular screening'), irrespective of whether this screening history was consistent with NCSP guidelines. In particular, the cases included some women who would have been too old or too young to have received recent or any screening (if following NCSP guidelines) prior to their diagnosis. Furthermore, it is possible that women have been categorized as 'regular screening' when actually they should have received smears more frequently than once every 3 years (e.g. if they had had a high-grade abnormality) if they had been following NCSP guidelines. However, any such discrepancies would have led to a reduction in the protective effect of regular screening found in this study. Conversely, the methodology did not distinguish whether a woman had been rescreened in an interval that was shorter than the standard recommended 3 years. Women being screened more frequently in this manner would potentially increase the protective effect of regular screening.

Bearing these strengths and limitations of the data in mind, there are three main findings of this study. First, more than half of the women diagnosed with cervical cancer in New Zealand during 1994–2005 had not been screened >6 months before diagnosis. Secondly, women who were regularly screened had a considerably lower risk of being diagnosed at a late stage. Thirdly, screening history did not appear to explain the ethnic differences in stage at diagnosis.

The first major finding of the study is that the screening rates were relatively low in the cervical cancer cases (Table 1) compared with the rates in the general population for 2001 (no national data are available prior to this) to 2006.[4,22,28–31] More than half (56.7%) of the women had not had a screening smear. This study did not include matched controls without cervical cancer, but information for the general population is available from monitoring reports for the NCSP.[4,22,28–31] Overall, 43.3% of cervical cancer cases had been screened ('ever screened'), compared with ~93% in the general population in 2001.[22] Of the cervical cancer cases that had been 'ever screened', 19.7% had 'irregular screening—participation' compared with ~87% in the general population in 2001,[22] 42.4% had 'irregular screening—coverage' compared with 72.7% in the general population in 2001,[22] and 32.2% had 'regular screening' (the NCSP monitoring reports do not include 'regular' screening, to the authors' knowledge there is no published information about this in the general population).

These findings are consistent with those of previous studies in other countries which have shown that unscreened women have a higher rate of invasive cervical cancer, and conversely that women with cervical cancer have been screened less often than (hospital) control women or those in the general population.[32–35] No record of screening prior to diagnosis was found for 56.7% of the cases included in the current study, a finding that is similar to the estimates of 53–68% reported in other recent studies.[20,33,35] Screening was particularly low in women with squamous cell carcinoma (41.3%) or adenosquamous cell carcinoma (36.8%), compared with cases of adenocarcinoma (59.7%), a finding which is consistent with previous evidence that screening is less effective for precursors of adenocarcinomas.[36–38]

The second major finding of the study is that screening history was associated with stage at diagnosis (Table 2). Women that were regularly screened (compared with women that had no screening smears) had a reduced risk of a late-stage diagnosis (compared with early-stage diagnosis) (OR 0.16, 95% CI 0.10–0.26). Women that met even the weak criterion of 'irregular screening—participation' had a reduced risk (OR 0.17, 95% CI 0.10–0.31). The apparent 'protective effect' of 'diagnostic only' screens is

Table 3 Odds ratios for ethnicity, NZDep, urban/rural residence and late-stage diagnosis (stages II–IV) versus early-stage diagnosis (stages 0–IB2)

	All cases		Squamous cell carcinoma		Adenocarcinoma[a]	
	Adjusted for age, registration year and other variables in table	Adjusted for age, registration year, other variables in table and screening history	Adjusted for age, registration year and other variables in table	Adjusted for age, registration year, other variables in table and screening history	Adjusted for age, registration year and other variables in table	Adjusted for age, registration year, other variables in table and screening history
Ethnicity						
Other	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]
Māori	2.72 (1.99–3.72)	2.45 (1.77–3.39)	2.73 (1.93–3.88)	2.42 (1.68–3.49)	2.10 (0.96–4.57)	1.93 (0.86–4.33)
Pacific	1.45 (0.81–2.61)	0.99 (0.54–1.81)	1.44 (0.75–2.77)	0.95 (0.49–1.88)	2.51 (0.61–10.35)	2.26 (0.51–10.06)
Asian	1.00 (0.59–1.69)	0.92 (0.53–1.57)	0.73 (0.39–1.36)	0.69 (0.36–1.31)	2.81 (0.98–8.06)	2.62 (0.88–7.81)
NZDep2001 (quintiles)						
1 (least deprived)	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]
2	0.89 (0.56–1.40)	0.88 (0.55–1.42)	0.87 (0.52–1.46)	0.88 (0.51–1.51)	0.90 (0.30–2.70)	1.00 (0.32–3.09)
3	1.27 (0.83–1.94)	1.24 (0.79–1.92)	1.19 (0.73–1.94)	1.21 (0.72–2.02)	1.83 (0.70–4.76)	1.83 (0.68–4.94)
4	1.26 (0.84–1.89)	1.22 (0.80–1.86)	1.16 (0.73–1.83)	1.21 (0.75–1.95)	1.91 (0.72–5.12)	1.82 (0.66–5.07)
5 (most deprived)	1.10 (0.73–1.65)	1.11 (0.72–1.69)	1.00 (0.63–1.59)	1.06 (0.66–1.72)	1.73 (0.64–4.65)	1.82 (0.65–5.10)
Urban/rural residence						
Main urban	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]	1.00[b]
Secondary urban	0.96 (0.69–1.33)	0.95 (0.67–1.33)	1.02 (0.71–1.46)	1.04 (0.72–1.53)	0.67 (0.28–1.57)	0.55 (0.22–1.35)
Rural	0.98 (0.65–1.50)	1.00 (0.65–1.55)	1.01 (0.63–1.61)	1.03 (0.63–1.68)	0.76 (0.25–2.36)	0.72 (0.22–2.36)

[a]Adenocarcinoma including adenosquamous carcinoma.
[b]Reference category.
NZDep 2001: New Zealand Deprivation Index 2001.

difficult to interpret, since the 'diagnostic-only' cases probably comprise two distinct groups—those who genuinely only had a diagnostic smear and those who had a screening smear. This may explain why the finding for 'diagnostic-only' screens (OR 0.39) lies between that for 'regular screening' (OR 0.16) and 'no screening' (the reference category with an OR of 1.0).

As previously stated, there is evidence that screening for precursors for adenocarcinomas is less effective than screening for squamous cell carcinomas.[36–38] It is therefore interesting that in the current study the effect (on the OR) of 'regular screening' was stronger in the cases of squamous cell carcinoma (OR 0.12, 95% CI 0.07–0.23) than in the cases of adenocarcinoma (OR 0.32, 95% CI 0.13–0.82), but the effect was still strong in the latter group. This is consistent with the finding of Sasieni and Adams that cervical screening seems to have had a substantial impact on the rate of adenocarcinoma in younger women.[39]

The third major set of findings involves the ethnic differences in screening history (Table 1) and stage at diagnosis (Table 3). Rates of 'participation' (a cytology or histology result recorded on the NCSP-R in the previous 6 years) in the NCSP are substantially lower for Māori and Pacific women (e.g. in 2006, 62.4 and 60.4%, respectively) than for non-Māori, non-Pacific women (91.4%) and this is reflected in the lower percentage of screened women of these ethnicities in the current study.[4] The percentages 'ever screened' were 24.8% in Pacific women, 30.5% in Asian, 40.6% in Māori and 46.1% in 'Other'. The corresponding estimates for 'regular screening' were 5.7, 7.8, 12.5 and 15.3% (Table 1).

The current study found that 21.4% of Māori cases had not had a smear prior to their cancer diagnosis, compared with 54% in the study by Ratima *et al.*,[40] which included cases that had occurred before (and in the first 2 years after) the NCSP was established. However, the current study found that an additional 38% of Māori women had only had a smear in the 6 months prior to diagnosis, thus suggesting that 59.4% of Māori women had not been 'ever screened'.

Despite the ethnic differences in screening history, adjustment for screening history did not entirely account for the ethnic differences in stage at diagnosis (Table 3). For example, the OR for a late-stage diagnosis in Māori women (compared with 'Other' women) decreased only from 2.72 (95% CI 1.99–3.72) to 2.45 (95% CI 1.77–3.39) when adjusted for screening history. In contrast, the increased risk of late-stage diagnosis in Pacific women (compared with 'Other' women; OR 1.45, 95% CI 0.81–2.61) disappeared when adjusted for screening history (OR 0.99, 0.54–1.81). These data therefore indicate that there is a large excess risk of late-stage diagnosis in Māori women that is not explained by differences in screening history, whereas there is a small excess risk of late-stage diagnosis in Pacific women, which is explained by differences in screening history.

The study was not able to examine the importance of other aetiological factors for cervical cancer survival. Since screening history did not completely explain the ethnic differences in stage at diagnosis, it is important that other possible explanations for these differences should be explored in further studies. These may include delayed diagnosis, i.e. some women with regular screening histories may have a longer period of time between a smear that is suggestive of cancer (or the onset of symptoms) and actual diagnosis of cancer. The reasons for delayed diagnosis and non-participation in screening are complex, but may include barriers to accessing health care (such as language, culture, income and/or education level, and patient–doctor relationship).[41] There is also some evidence that in New Zealand racial discrimination is associated with poorer self-rated health,[42,43] but there appears to be no evidence directly related to the cervical cancer care pathway in New Zealand. There is some evidence[4,22,28–31] that histological test results for Māori and Pacific women are reported after a longer period of time than those for non-Māori, non-Pacific women, although it is unclear whether this time difference would actually lead to a late stage at diagnosis since the precursor lesions are known to exist for several years. Failure to be invited or to return for a repeat smear after an unsatisfactory result, or to have a histological specimen taken after a high-grade smear, or a delay in seeing a gynaecologist, as well as not reporting symptoms, may also lead to a delay, resulting in a late stage at diagnosis.[4,22,28–31,40]

Conclusions

In conclusion, more than half of the women diagnosed with cervical cancer in New Zealand during 1994–2005 had not been screened >6 months before diagnosis. Women that were regularly screened had a considerably lower risk of being diagnosed at a late stage, and screening history did not appear to explain the ethnic differences in stage at diagnosis. These findings indicate that in order to reduce further the proportion of women who are diagnosed with cervical cancer at a late stage, major efforts should continue to increase the proportion of women who participate in the NCSP and to encourage women to participate in the screening programme on a regular basis. Further investigation is required to elucidate the reasons for the increased risk of a late-stage diagnosis in Māori women that persists after adjustment for screening history, SES and urban/rural residence.

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Conflict of interest: None declared.

KEY MESSAGES

- More than one-half of women diagnosed with cervical cancer in New Zealand during 1994–2005 had not been screened prior to 6 months before diagnosis.
- Women that were regularly screened had a considerably lower risk of being diagnosed at a late stage.
- However, differences in screening history did not account for the previously reported Māori/non-Māori differences in stage at diagnosis.

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APPENDIX 4

Comorbidity and cervical cancer survival in NZ

MASSEY UNIVERSITY
GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION TO DOCTORAL THESIS CONTAINING PUBLICATIONS

(To appear at the end of each thesis chapter/section/appendix submitted as an article/paper or collected as an appendix at the end of the thesis)

We, the candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of Candidate: NAOMI BREWER

Name/Title of Principal Supervisor: ASSOCIATE PROFESSOR BARRY BORMAN

Name of Published Research Output and full reference: Does comorbidity explain the ethnic inequalities in cervical cancer survival in New Zealand? A retrospective cohort study. BMC Cancer 2011; 11:132

In which Chapter is the Published Work: CHAPTER FOUR

Please indicate either:

- **The percentage of the Published Work that was contributed by the candidate:** 85%
  and / or
- **Describe the contribution that the candidate has made to the Published Work:**

A Brewer
Candidate's Signature

2/11/11
Date

Principal Supervisor's signature

2/11/11
Date

BMC Cancer

RESEARCH ARTICLE Open Access

Does comorbidity explain the ethnic inequalities in cervical cancer survival in New Zealand? A retrospective cohort study

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Abstract

Background: There are large ethnic differences in cervical cancer survival in New Zealand that are only partly explained by stage at diagnosis. We investigated the association of comorbidity with cervical cancer survival, and whether comorbidity accounted for the previously observed ethnic differences in survival.

Methods: The study involved 1,594 cervical cancer cases registered during 1994-2005. Comorbidity was measured using hospital events data and was classified using the Elixhauser instrument; effects on survival of individual comorbid conditions from the Elixhauser instrument were also assessed. Cox regression was used to estimate adjusted cervical cancer mortality hazard ratios (HRs).

Results: Comorbidity during the year before diagnosis was associated with cervical cancer-specific survival: those with an Elixhauser count of ≥3 (compared with a count of zero) had a HR of 2.17 (1.32-3.56). The HR per unit of Elixhauser count was 1.25 (1.11-1.40). However, adjustment for the Elixhauser instrument made no difference to the mortality HRs for Māori and Asian women (compared to 'Other' women), and made only a trivial difference to that for Pacific women. In contrast, concurrent adjustment for 12 individual comorbid conditions from the Elixhauser instrument reduced the Māori HR from 1.56 (1.19-2.05) to 1.44 (1.09-1.89), *i.e.* a reduction in the excess risk of 21%; and reduced the Pacific HR from 1.95 (1.21-3.13) to 1.62 (0.98-2.68), *i.e.* a reduction in the excess risk of 35%.

Conclusions: Comorbidity is associated with cervical cancer-specific survival in New Zealand, but accounts for only a moderate proportion of the ethnic differences in survival.

Background

In 2005, cervical cancer was the ninth most common site of cancer registration for New Zealand females [1], and the incidence and mortality rates were moderately high compared with the rest of the developed world [2]. Incidence and mortality rates are not the same across ethnic groups within New Zealand. For example, in 2005, Māori women had an incidence rate of 9.0, Pacific women 16.3 and 'Other' (predominantly European) women 5.6 per 100,000 women; Māori women had a mortality rate of 6.5, Pacific women 7.1 and 'Other' women 1.4 per 100,000 women [1].

We have previously reported demographic differences in cervical cancer survival in New Zealand [3]. Māori and Pacific women had higher death rates than 'Other' women, whereas Asian women had a lower risk. Adjustment for stage at diagnosis, socio-economic position (SEP), and urban/rural residence explained only some of the increased risks in Māori and Pacific women. Ethnic differences in stage at diagnosis were not entirely explained by differences in screening history [4,5]. There is some evidence of limited differences in treatment between Māori and non-Māori women, but these differences have little impact on survival differences [6]. Thus, the reasons for the differences in survival are currently unclear, but one possibility not previously examined is that they may, in part, be due to differences in comorbidity at the time of cervical cancer diagnosis. Māori and Pacific women have higher rates of many diseases, including smoking-related respiratory diseases, diabetes and cardiovascular disease [7-9]. Such comorbid conditions may have effects prior to diagnosis (*e.g.*

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influence the likelihood of cancer screening or late-stage diagnosis) [10,11], or affect survival post-diagnosis either directly (*e.g.* some comorbid conditions may adversely affect prognosis) or indirectly (*e.g.* some comorbid conditions may affect or limit treatment options or decisions). In New Zealand, comorbidity has been found to contribute to ethnic-specific survival disparities for colon cancer [12], the management of stages I and II non-small-cell lung cancer [13], and adverse event status, inpatient death and increased length of stay in selected Auckland hospitals [14]. Internationally comorbidity has also been found to adversely affect survival in patients with a range of conditions, including cervical cancer [15-21].

We therefore investigated the associations of various comorbid conditions with cervical cancer survival, and whether these comorbid conditions accounted for the previously observed ethnic differences in survival.

Methods

The source population comprised all cervical cancer cases registered with the New Zealand Cancer Registry (NZCR) between 1 January 1994 and 30 December 2005 [3,4]. The NZCR records self-identified ethnicity, and allows for multiple responses. Participants who reported more than one ethnicity were classified into a single ethnicity using the standard system of prioritisation: Māori > Pacific > Asian > 'Other' [22]. Participants with missing ethnicity data were included in the 'Other' (predominantly European) ethnic group in the analyses. This approach is standard practice in New Zealand health research [23,24]. All registrations include the National Health Index (NHI) number which uniquely identifies individual health care users; this was used to obtain cause-specific mortality data (from the Mortality Collection) up to the end of December 2005 (the most recent year for which data was available), and hospital events data (from the National Minimum Dataset (NMDS); up to 99 diagnosis/procedure codes may be provided to the NMDS) from 1988 to 31 December 2005.

SEP was estimated using the New Zealand Deprivation Index 2001 (NZDep), an area-based measure derived from a combination of nine socioeconomic variables derived from the national census [25]. Each participant was assigned a score based upon the residential area (the domicile code) in which they lived, as recorded on the NZCR at the time of registration. These scores were then grouped into quintiles [25].

The domicile code recorded for each participant was also used to assign urban/rural residence according to population size [26]. Participants were classified as living in a main urban area (with a population of ≥30,000), a secondary or minor urban area (population ≥1,000 to 29,999), or a rural area (population <1,000).

Data on stage at diagnosis were obtained from the NZCR, and reported using the International Federation of Gynecology and Obstetrics (FIGO) system [27]. In order to provide sufficient numbers in each category, the FIGO stages were grouped into four categories: stages 0 to IB2; II to IIB; III to IIIB; IVA to IVB. A fifth category of 'missing' was utilised for cases where the FIGO stage was unknown. We conducted a basic sensitivity analysis, to assess the potential for bias resulting from the exclusion of the women with missing stage data; this involved three sets of analyses: (i) adjusting for stage and excluding the women with missing stage data; (ii) including the women with and without missing stage data, and adjusting for stage with a dummy variable representing the women with missing stage data; and (iii) including the women with and without missing stage data, but not adjusting for stage. The three sets of analyses yielded the same patterns. We therefore present here the findings from the first method (i.e. excluding women with missing stage), because it is necessary to adjust for stage, and this is the only approach that enables us to do this validly [3,4].

We used two widely utilised comorbidity measures. The Elixhauser instrument [28] was designed specifically for use with administrative data, and is based on a set of 30 comorbid conditions which were associated with increased length of stay, hospital charges and mortality among non-maternal inpatients in California in 1992 [28]. The Charlson Comorbidity Index (CCI) [29] comprises 19 comorbid conditions which are given a weight of 1 to 6 on the basis of the strength of their association with one-year mortality among a cohort of 607 general medical patients in the United States [29]. To our knowledge this is the first study of the role of comorbidity in cervical cancer survival in New Zealand, and there was therefore no prior data on which of these two (or any other) comorbidity measures were most appropriate to use. In general, we found very similar results with the two comorbidity measures, and we have therefore only reported the findings for the Elixhauser instrument (the findings for the CCI are available as Additional file 1 Tables S1-S4); effects on survival of individual comorbid conditions from the Elixhauser instrument were also assessed.

Comorbidity was assessed, using the hospital events data, according to the enhanced ICD-9-CM (for data from 1988-1999) and ICD-10 (for data from 2000-2005) coding algorithms of Quan *et al* [30] for the Elixhauser instrument [28] and the CCI [29]. We used both the primary and the secondary diagnoses fields to identify comorbid conditions during the period one year, and the period five years, preceding, and including, the date of diagnosis. The optimal look-back period (the time over which to identify comorbid conditions) was not

clear since shorter times may capture more active conditions and longer periods may be more likely to identify all of the important comorbid conditions [31]. We therefore utilised two look-back periods, with five years being the longest timeframe over which we had data for all of the women. In general, we found similar results with the two look-back periods (see Additional file 1 Tables S1-S3), though the associations of comorbidity with survival were somewhat stronger when using the one-year look-back period; we therefore only report here the findings for the one-year look-back period. We included comorbid conditions identified up to and including the date of diagnosis to strike a balance between identifying all of the comorbid conditions that the women had at the time of diagnosis whilst attempting to avoid including conditions that may have been caused by treatment after diagnosis. Metastatic solid tumours were excluded from both comorbidity algorithms, as were all diagnosis codes for cervical cancer. For each woman, the comorbidity frequency (for the Elixhauser instrument) and score (for the CCI) were recorded (for use as continuous variables) and were also then categorised into (two sets of) four groups (0, 1, 2, and ≥3).

The Elixhauser measure was calculated using the Statistical Analysis System (SAS) software 9.1, whilst all other analyses were conducted using Intercooled Stata 10 for Windows (StataCorp, College Station, Texas, USA). The Cox proportional hazards model [32] was used to estimate the hazard ratios (HRs) for cervical cancer mortality, 'other mortality' (non-cervical cancer), and total mortality associated with the Elixhauser count, as well as with ethnicity, NZDep, and urban/rural residence, adjusted for age, registration year, and stage at diagnosis. Women were censored at the time of their death or on 31 December 2005 if they were still alive at that time [3]. In the final set of analyses, the HRs for each ethnic group were estimated adjusted for the Elixhauser count, and, finally, for the individual comorbid conditions that had a HR of ≥1.5.

The New Zealand Central Ethics Committee granted ethical approval for the study (CEN/08/04/EXP).

Results

There were 2,323 cases of cervical cancer registered on the NZCR between 1 January 1994 and 31 December 2005, and all of these cases were included in the descriptive analyses of comorbidity (Table 1). Using a one-year look-back period, 15.6% of cases had had at least one comorbidity (included in the Elixhauser instrument) event in the year before diagnosis; the percentages were similar in Asian (13.3%) and 'Other' women (13.7%), but were highest in Pacific women (32.4%), with Māori women having an intermediate value (19.7%). The Elixhauser count was strongly associated with NZDep, and FIGO stage, but was only weakly associated with urban/rural residence and time period of diagnosis.

Table 1 Characteristics of cervical cancer cases, n (%)

		Elixhauser co-morbidities			
	Total	0	1	2	3+
Total	2,323 (100)	1,960 (84.4)	223 (9.6)	63 (2.7)	77 (3.3)
FIGO stage					
0 to IB2	1,155 (49.7)	1,067 (92.4)	63 (5.5)	13 (1.1)	12 (1.0)*
II to IIB	262 (11.3)	207 (79.0)	32 (12.2)	11 (4.2)	12 (4.6)
III to IIIB	232 (10.0)	169 (72.8)	41 (17.7)	16 (6.9)	6 (2.6)
IVA to IVB	53 (2.3)	33 (62.3)	11 (20.8)	3 (5.7)	6 (11.3)
Missing	621 (26.7)	484 (77.9)	76 (12.2)	20 (3.2)	41 (6.6)
Ethnicity					
Other	1,674 (72.1)	1,444 (86.3)	141 (8.4)	41 (2.5)	48 (2.9)*
Māori	416 (17.9)	334 (80.3)	50 (12.0)	15 (3.6)	17 (4.1)
Pacific	105 (4.5)	71 (67.6)	21 (20.0)	3 (2.9)	10 (9.5)
Asian	128 (5.5)	111 (86.7)	11 (8.6)	4 (3.1)	2 (1.6)
NZDep2001, quintiles					
1 (Least deprived)	298 (12.8)	277 (93.0)	14 (4.7)	3 (1.0)	4 (1.3)**
2	333 (14.3)	283 (85.0)	33 (9.9)	8 (2.4)	9 (2.7)
3	416 (17.9)	350 (84.1)	37 (8.9)	12 (2.9)	17 (4.1)
4	526 (22.6)	432 (82.1)	56 (10.7)	19 (3.6)	19 (3.6)
5 (Most deprived)	623 (26.8)	510 (81.9)	67 (10.8)	21 (3.4)	25 (4.0)
Missing	127 (5.5)	108 (85.0)	16 (12.6)	0	3 (2.4)
Urban/rural residency					
Main urban	1,640 (70.6)	1,403 (85.6)	141 (8.6)	42 (2.6)	54 (3.3)[NS]
Secondary urban	361 (15.5)	288 (79.8)	47 (13.0)	13 (3.6)	13 (3.6)
Rural	196 (8.4)	162 (82.7)	19 (9.7)	8 (4.1)	7 (3.6)
Missing	126 (5.4)	107 (84.9)	16 (12.7)	0	3 (2.4)
Year of diagnosis					
1994-1997	843 (36.3)	714 (84.7)	82 (9.7)	24 (2.9)	23 (2.7)[NS]
1998-2001	815 (35.1)	689 (84.5)	79 (9.7)	20 (2.5)	27 (3.3)
2002-2005	665 (28.6)	557 (83.8)	62 (9.3)	19 (2.9)	27 (4.1)

p value based on Pearson's chi-squared

* p = 0.0001

** p = 0.02

NS: Not significant at 95%

For the analyses of the effects of comorbidity on mortality (Table 2), the following exclusions were made; 621 because they did not have a FIGO code (including 17 women whose cancer registration was made on the date of the their death, and 50 women that could not be assigned an NZDep score), 77 cases because they did not have a domicile code that could be assigned an NZDep score, and a further 31 cases because they were diagnosed after 30 June 2005 (and therefore had a potential follow-up time of less than six months),

Table 2 Mortality by comorbidity

Comorbidity	HR (95%CI)[a]
Cervical cancer	
Elixhauser (1 unit)	1.25 (1.11-1.40)
Elixhauser 0	1.00[b]
Elixhauser 1	1.29 (0.96-1.75)
Elixhauser 2	1.33 (0.83-2.13)
Elixhauser 3+	2.17 (1.32-3.56)
Other mortality (not cervical cancer)	
Elixhauser (1 unit)	1.46 (1.18-1.79)
Elixhauser 0	1.00[b]
Elixhauser 1	2.49 (1.39-4.44)
Elixhauser 2	2.62 (1.20-5.72)
Elixhauser 3+	2.76 (1.04-7.30)
Total mortality	
Elixhauser (1 unit)	1.28 (1.15-1.41)
Elixhauser 0	1.00[b]
Elixhauser 1	1.47 (1.13-1.92)
Elixhauser 2	1.48 (0.99-2.21)
Elixhauser 3+	2.20 (1.41-3.41)

[a] Adjusted for age, year of diagnosis, stage, ethnicity, socioeconomic position, and urban/rural residence

[b] Reference category

leaving 1,594 women to be included in the analyses. The women that were excluded because they did not have a FIGO code had a similar ethnic and SEP distribution to the cases that did have a FIGO code [4].

Of the 1,594 women included in the analyses: 99.2% were diagnosed based upon the histology of the primary malignant tumour [3]; 1,163 (73%) identified as 'Other' ethnicity, 312 of whom died during the follow-up period, 241 (77%) due to cervical cancer, and 71 (23%) due to other causes; 292 identified as Māori ethnicity (18%), 104 of whom died, 92 (88%) due to cervical cancer, and 12 (12%) due to other causes; 59 (4%) identified as Pacific ethnicity, 20 of whom died, 20 (100%) due to cervical cancer; and, 80 (5%) identified as Asian ethnicity, 14 of whom died, 13 (93%) due to cervical cancer, and 1 (7%) due to other causes.

Table 2 shows the HRs for cervical cancer survival by comorbidity, adjusted for age, year of diagnosis, stage, ethnicity, NZDep, and urban/rural residence. Comorbid disease in the year before diagnosis was associated with cervical cancer-specific survival: those with an Elixhauser count of 3 or more had a HR of 2.17 (1.32-3.56). The HR was associated with a per unit increase (when analysing the Elixhauser instrument as a continuous variable) of 1.25 (1.11-1.40). Comorbidity was more strongly associated with mortality from conditions other than cervical cancer: those with an Elixhauser count of 3 or more had a HR for other mortality of 2.76 (1.04-7.30). The HR was associated with a per unit increase of 1.46 (1.18-1.79).

We estimated the cervical cancer-specific survival HRs adjusted for age, year of diagnosis, stage, ethnicity, NZDep and urban/rural residence, for those with individual conditions included in the Elixhauser instrument (see Additional file 1 Table S3). Thirteen of the individual comorbid conditions showed HRs of ≥1.5 in the one-year look-back period; congestive heart failure (2.35 95% CI 1.22-4.52), valvular disease (2.84, 0.70-11.61), complicated hypertension (1.74, 0.24-12.72), chronic pulmonary disease (1.62, 0.95-2.77), uncomplicated diabetes (2.17, 1.33-3.53), complicated diabetes (10.46, 3.01-36.37), renal failure (4.27, 2.08-8.76), liver disease (2.43, 0.76-7.78), coagulopathy (2.78, 0.68-11.43), obesity (3.52, 1.55-7.98), fluid and electrolyte disorders (4.03, 2.01-8.08), blood loss anaemia (2.44, 1.48-4.00), and drug abuse (3.28, 0.45-23.76). We therefore adjusted for these individual comorbid conditions in the final analyses, except for uncomplicated diabetes because the methodology of the Elixhauser instrument allows for a woman to be recorded as having both uncomplicated and complicated diabetes (where the Elixhauser count was used, only complicated diabetes (or complicated hypertension) was included when the woman also had uncomplicated diabetes (or uncomplicated hypertension)).

Table 3 shows the findings for ethnic differences in cervical cancer-specific survival adjusted for comorbidity as a continuous variable and for the 12 individual comorbid conditions. Adjustment for the Elixhauser count made no difference to the cervical cancer-specific survival HRs for Māori and Asian women (compared to 'Other' women), and made only a trivial difference to that for Pacific women. The largest change was for Pacific women, where the HR fell from 1.95 (1.21-3.13) to 1.92 (1.20-3.09). However, the HRs changed more substantially when adjustment was made for all 12 of the individual comorbid conditions; the HR for Māori women fell from 1.56 (1.19-2.05) to 1.44 (1.09-1.89), representing a 21% decrease in the excess mortality risk; the HR for Pacific women fell from 1.95 (1.21-3.13) to 1.62 (0.98-2.68), representing a 35% decrease in the excess mortality risk.

Discussion

This study found that comorbidity is associated with cervical cancer-specific mortality and more strongly with mortality from other causes. This latter finding is not surprising since some cervical cancer patients who have a comorbidity may die from this comorbidity, and this group would therefore be expected to have a higher death rate from "other causes" (i.e. all causes of death other than cervical cancer) than cervical cancer patients who do not have a comorbidity.

Adjusting for the Elixhauser instrument produced little change in the ethnic differences in mortality. In

Table 3 Cervical cancer-specific mortality by ethnicity adjusted for comorbidity

		Ethnicity			
Comorbidities	**Comorbidity**	**Other**	**Māori**	**Pacific**	**Asian**
	HR (95%CI)[a]	**HR (95%CI)[b]**	**HR (95%CI)[c]**	**HR (95%CI)[c]**	**HR (95%CI)[c]**
No comorbidity adjustment/inclusion		1.00	1.56 (1.19-2.05)	1.95 (1.21-3.13)	0.72 (0.41-1.27)
Elixhauser as continuous variable	1.25 (1.11-1.40)	1.00	1.55 (1.19-2.04)	1.92 (1.20-3.09)	0.72 (0.41-1.26)
Individual comorbities					
Congestive heart failure	2.35 (1.22-4.52)	1.00	1.57 (1.20-2.06)	1.98 (1.23-3.17)	0.72 (0.41-1.27)
Valvular disease	2.84 (0.70-11.61)	1.00	1.56 (1.19-2.04)	1.96 (1.22-3.14)	0.72 (0.41-1.27)
Hypertension, complicated	1.74 (0.24-12.72)	1.00	1.57 (1.19-2.06)	1.95 (1.22-3.13)	0.72 (0.41-1.27)
Chronic pulmonary disease	1.62 (0.95-2.77)	1.00	1.55 (1.18-2.03)	1.95 (1.22-3.13)	0.67 (0.38-1.19)
Diabetes, complicated	10.46 (3.01-36.37)	1.00	1.55 (1.18-2.04)	1.70 (1.03-2.80)	0.71 (0.40-1.25)
Renal failure	4.27 (2.08-8.76)	1.00	1.58 (1.20-2.07)	1.70 (1.04-2.77)	0.72 (0.41-1.27)
Liver disease	2.43 (0.76-7.78)	1.00	1.55 (1.18-2.03)	1.92 (1.20-3.09)	0.72 (0.41-1.26)
Coagulopathy	2.78 (0.68-11.43)	1.00	1.55 (1.18-2.03)	1.91 (1.19-3.07)	0.72 (0.41-1.27)
Obesity	3.52 (1.55-7.98)	1.00	1.55 (1.18-2.04)	1.90 (1.18-3.05)	0.72 (0.41-1.27)
Fluid and electrolyte disorders	4.03 (2.01-8.08)	1.00	1.51 (1.15-1.98)	1.97 (1.23-3.16)	0.69 (0.39-1.21)
Blood loss anaemia	2.44 (1.48-4.00)	1.00	1.53 (1.17-2.01)	1.98 (1.23-3.17)	0.71 (0.40-1.26)
Drug abuse	3.28 (0.45-23.76)	1.00	1.56 (1.19-2.04)	1.95 (1.22-3.13)	0.72 (0.41-1.27)
Multivariate - all 12 of the above		1.00	1.44 (1.09-1.89)	1.62 (0.98-2.68)	0.63 (0.35-1.13)

[a] Adjusted for age, year of diagnosis, stage, ethnicity, socioeconomic position, and urban/rural residence

[b] Reference category

[c] Adjusted for age, year of diagnosis, stage, ethnicity, socioeconomic position, urban/rural residence, and comorbidity index

contrast, adjustment for 12 individual comorbid conditions included in the Elixhauser instrument reduced the excess HR for Māori women by 21% and for Pacific women by 35%.

A strength of the study is that the Cancer Registry Act came into effect in 1994 making cancer registration mandatory [1], and case under-ascertainment unlikely [23]. Death registration is also mandatory in New Zealand, and can be linked to cancer registrations using the NHI number; thus there is a high probability that the study identified all of the cases that died in New Zealand. There may have been some misclassification of cause of death, but it is unlikely to have produced significant bias in the ethnic comparisons [33]. Furthermore, classification of the cause of death for patients on the NZCR is highly accurate since in cases that are registered prior to death, information from the Cancer Registry is used to classify the underlying cause of death [34].

Other possible limitations of the study include the potential misclassification of ethnicity, which has been estimated to produce a 17% undercount of Māori cancer registrations [35] (this involves misclassification of ethnicity on registrations, rather than case under-ascertainment). Thus, the 'Other' ethnic group may contain some Māori cases that were incorrectly classified, thereby diluting the ethnic survival differences. There is also evidence of a 6-7% undercount of Māori deaths [35,36], but this would not bias the current study since the ethnicity recorded on the Cancer Registry was used in all analyses. The classification of ethnicity was based on the wording of the corresponding census questions, and these have changed over time, but once again this is unlikely to have produced serious bias because the ethnicity recorded on the Cancer Registry was also used to classify the corresponding deaths, and the analyses were adjusted for year of diagnosis. There may also be misclassification of area-based SEP and urban/rural residence in cancer registrations, but in each instance, any such misclassification is unlikely to be associated with subsequent survival and, if anything, is likely to produce underestimates of the differences in survival between these various demographic groups.

The greatest change in the ethnic-specific HRs occurred when adjustment was made for the 12 individual comorbid conditions, rather than using the summary Elixhauser comorbidity measure. Some of these individual comorbid conditions may have shown elevated HRs by chance, because of the large number of comparisons involved.

The comorbidity data was based on administrative in-hospital data and therefore some conditions may not have been recorded. However, a study on colon cancer in New Zealand found that despite comorbid conditions being recorded more frequently in patients' medical notes than in administrative data, the use of a comorbidity measure still improved the prediction of all-cause survival in a multivariable model [37]. It is also possible that some patients

had undiagnosed disease, but misclassification of this type would probably decrease the effect of comorbidity on survival [37].

To date, there have been few studies of the role of comorbid conditions in cervical cancer survival, and none in New Zealand. Our results are generally consistent with those of Coker et al. [15] who found that in Texan women aged 65 years or older with cervical cancer, those that had one or more comorbid conditions were 40% more likely to die (from all causes) compared with women who did not have any comorbid conditions. However, unlike Coker et al. [15] who did not find an independent association between comorbidity and cervical cancer-specific survival, we found an independent 25% increased risk of death from cervical cancer for each unit increase of the Elixhauser count (Table 3). In a study of stage IB squamous cell carcinoma, Hopkins and Morley [17] found that women with diabetes had an 82% cumulative 5-year all-cause survival compared with an 89% survival in those who did not have diabetes (p = 0.04). These findings are also consistent with the 10-fold increased risk of cervical cancer-specific mortality in the present study. In contrast to our study, Leath et al. [38] did not find comorbid conditions to be an independent predictor of survival in women with either early or late stage cervical cancer.

The present study has shown that Māori and Pacific women have a larger number of comorbid conditions than 'Other' and Asian women when measured with the Elixhauser instrument with a one-year look-back period (Table 1). Women living in more deprived areas had larger numbers of comorbid conditions according to the Elixhauser instrument. We found independent associations between the Elixhauser count and cervical cancer-specific, 'other' and total mortality (Table 2).

Reducing ethnic inequalities in cancer is one of the overall purposes of the New Zealand Cancer Control Strategy [39]. We and others [1,3,40,41] have previously demonstrated substantial ethnic inequalities in cervical cancer incidence, mortality and survival in New Zealand. It has been suggested [42] that comorbid conditions, which are known to differ between ethnic groups [7], could account for these inequalities and, as mentioned earlier, there is some international evidence of comorbidity adversely affecting cervical cancer survival [15,17,18]. The current study, the first to empirically investigate this issue in New Zealand, only partially supports this hypothesis. It is possible that there are small ethnic differences at each stage of the cancer continuum (screening, diagnosis, treatment, comorbidity, follow-up, etc) and that each of these makes a small contribution to the major overall ethnic differences in survival that we have reported.

Conclusion

In summary, we assessed the roles of comorbid conditions identified through hospital events data and found that these conditions are associated with cervical cancer-specific mortality, but account for only a moderate proportion of the ethnic differences in survival. Other factors, including possible differences in treatment and follow-up, may also play a role.

Additional material

Additional file 1: Results for the Charlson Comorbidity Index and Elixhauser instrument with both the one-year and the five-year look-back periods. Table S1 Characteristics of cervical cancer cases; Table S2 Mortality by comorbidity measures; Table S3 Elixhauser comorbid conditions frequency and cervical cancer-specific mortality adjusted for individual comorbid conditions; Table S4 Cervical cancer-specific mortality by ethnicity adjusted for comorbidity with one-year look-back period.

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Authors' contributions

NB co-initiated and co-led the study design, collected the data, co-led the data analysis and interpretation, wrote the first draft of the paper, co-ordinated draft revisions and wrote the final manuscript. BB contributed to the study design, data analysis and interpretation, and draft revisions. DS contributed to the study design, data analysis and interpretation, and draft revisions. MJ contributed to the study conception and design, data analysis and interpretation, and draft revisions. STF contributed to the study design, data analysis and interpretation, and draft revisions. SC contributed to the data analysis and interpretation, and draft revisions. NP co-initiated and co-led the study design, co-led the data analysis and interpretation, and contributed to draft revisions. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Table S1: Characteristics of cervical cancer cases, n (%)

	Total	One-year look-back period								Five-year look-back period							
		Charlson Index				Elixhauser comorbid conditions				Charlson Index				Elixhauser comorbid conditions			
		0	1	2	3+	0	1	2	3+	0	1	2	3+	0	1	2	3+
Total	2,323 (100)	2,077 (89.4)	105 (4.5)	94 (4.1)	47 (2.0)	1,960 (84.4)	223 (9.6)	63 (2.7)	77 (3.3)	1,962 (84.5)	158 (6.8)	118 (5.1)	85 (3.7)	1,805 (77.7)	292 (12.6)	107 (4.6)	119 (5.1)
FIGO stage																	
0 to IB2	1,155 (49.7)	1,101 (95.3)	30 (2.6)	17 (1.5)	7 (0.6)$	1,067 (92.4)	63 (5.5)	13 (1.1)	12 (1.0)$	1,060 (91.8)	52 (4.5)	27 (2.3)	16 (1.4)$	1,000 (86.6)	96 (8.3)	37 (3.2)	22 (1.9)$
II to IIB	262 (11.3)	228 (87.0)	9 (3.4)	21 (8.0)	4 (1.5)	207 (79.0)	32 (12.2)	11 (4.2)	12 (4.6)	208 (79.4)	18 (6.9)	24 (9.2)	12 (4.6)	182 (69.5)	46 (17.6)	14 (5.3)	20 (7.6)
III to IIIB	232 (10.0)	191 (82.3)	22 (9.5)	15 (6.5)	4 (1.7)	169 (72.8)	41 (17.7)	16 (6.9)	6 (2.6)	177 (76.3)	29 (12.5)	18 (7.8)	8 (3.5)	154 (66.4)	47 (20.3)	18 (7.8)	13 (5.6)
IVA to IVB	53 (2.3)	38 (71.7)	5 (9.4)	4 (7.6)	6 (11.3)	33 (62.3)	11 (20.8)	3 (5.7)	6 (11.3)	36 (67.9)	7 (13.2)	4 (7.6)	6 (11.3)	30 (56.6)	12 (22.6)	5 (9.4)	6 (11.3)
Missing	621 (26.7)	519 (83.6)	39 (6.3)	37 (6.0)	26 (4.2)	484 (77.9)	76 (12.2)	20 (3.2)	41 (6.6)	481 (77.5)	52 (8.4)	45 (7.3)	43 (6.9)	439 (70.7)	91 (14.7)	33 (5.3)	58 (9.3)
Ethnicity																	
Other	1,674 (72.1)	1,513 (90.4)	69 (4.1)	67 (4.0)	25 (1.5)$	1,444 (86.3)	141 (8.4)	41 (2.5)	48 (2.9)$	1,427 (85.2)	109 (6.5)	84 (5.0)	54 (3.2)§	1,325 (79.2)	190 (11.4)	77 (4.6)	82 (4.9)*
Māori	416 (17.9)	363 (87.3)	22 (5.3)	20 (4.8)	11 (2.6)	334 (80.3)	50 (12.0)	15 (3.6)	17 (4.1)	341 (82.0)	32 (7.7)	25 (6.0)	18 (4.3)	308 (74.0)	64 (15.4)	20 (4.8)	24 (5.8)
Pacific	105 (4.5)	82 (78.1)	9 (8.6)	7 (6.7)	7 (6.7)	71 (67.6)	21 (20.0)	3 (2.9)	10 (9.5)	78 (74.3)	10 (9.5)	9 (8.6)	8 (7.6)	66 (62.9)	23 (21.9)	5 (4.8)	11 (10.5)
Asian	128 (5.5)	119 (93.0)	5 (3.9)	0	4 (3.1)	111 (86.7)	11 (8.6)	4 (3.1)	2 (1.6)	116 (90.6)	7 (5.5)	0	5 (3.9)	106 (82.8)	15 (11.7)	5 (3.9)	2 (1.6)
NZDep, quintiles																	
1 (Least deprived)	298 (12.8)	283 (95.0)	6 (2.0)	7 (2.4)	2 (0.7)NS	277 (93.0)	14 (4.7)	3 (1.0)	4 (1.3)§	269 (90.3)	13 (4.4)	10 (3.4)	6 (2.0)NS	261 (87.6)	19 (6.4)	11 (3.7)	7 (2.4)‡
2	333 (14.3)	294 (88.3)	18 (5.4)	14 (4.2)	7 (2.1)	283 (85.0)	33 (9.9)	8 (2.4)	9 (2.7)	282 (84.7)	22 (6.6)	17 (5.1)	12 (3.6)	266 (79.9)	41 (12.3)	12 (3.6)	14 (4.2)
3	416 (17.9)	369 (88.3)	22 (5.3)	14 (3.4)	11 (2.6)	350 (84.1)	37 (8.9)	12 (2.9)	17 (4.1)	349 (83.9)	30 (7.2)	17 (4.1)	20 (4.8)	325 (78.1)	43 (10.3)	21 (5.1)	27 (6.5)
4	526 (22.6)	459 (87.3)	29 (5.5)	30 (5.7)	8 (1.5)	432 (82.1)	56 (10.7)	19 (3.6)	19 (3.6)	430 (81.8)	43 (8.2)	32 (6.1)	21 (4.0)	391 (74.3)	78 (14.8)	28 (5.3)	29 (5.5)
5 (Most deprived)	623 (26.8)	559 (89.7)	22 (3.5)	24 (3.9)	18 (2.9)	510 (81.9)	67 (10.8)	21 (3.4)	25 (4.0)	525 (84.3)	41 (6.6)	34 (5.5)	23 (3.7)	463 (74.3)	92 (14.8)	31 (5.0)	37 (5.9)
Missing	127 (5.5)	113 (89.0)	8 (6.3)	5 (3.9)	1 (0.8)	108 (85.0)	16 (12.6)	0	3 (2.4)	107 (84.3)	9 (7.1)	8 (6.3)	3 (2.4)	99 (78.0)	19 (15.0)	4 (3.2)	5 (3.9)
Urban/rural residence																	
Main urban	1,640 (70.6)	1,488 (90.7)	62 (3.8)	54 (3.3)	36 (2.2)**	1,403 (85.6)	141 (8.6)	42 (2.6)	54 (3.3)NS	1,405 (85.7)	104 (6.3)	76 (4.6)	55 (3.4)NS	1,295 (79.0)	187 (11.4)	75 (4.6)	83 (5.1)NS
Secondary urban	361 (15.5)	306 (84.8)	20 (5.5)	26 (7.2)	9 (2.5)	288 (79.8)	47 (13.0)	13 (3.6)	13 (3.6)	288 (79.8)	28 (7.8)	25 (6.9)	20 (5.5)	262 (72.6)	63 (17.5)	17 (4.7)	19 (5.3)
Rural	196 (8.4)	171 (87.2)	15 (7.7)	9 (4.6)	1 (0.5)	162 (82.7)	19 (9.7)	8 (4.1)	7 (3.6)	163 (83.2)	17 (8.7)	9 (4.6)	7 (3.6)	150 (76.5)	23 (11.7)	11 (5.6)	12 (6.1)
Missing	126 (5.4)	112 (88.9)	8 (6.4)	5 (4.0)	1 (0.8)	107 (84.9)	16 (12.7)	0	3 (2.4)	106 (84.1)	9 (7.1)	8 (6.4)	3 (2.4)	98 (77.8)	19 (15.1)	4 (3.2)	5 (4.0)
Year of diagnosis																	
1994-1997	843 (36.3)	760 (90.2)	43 (5.1)	30 (3.6)	10 (1.2)§§	714 (84.7)	82 (9.7)	24 (2.9)	23 (2.7)NS	727 (86.2)	56 (6.6)	42 (5.0)	18 (2.1)NS	668 (79.2)	110 (13.1)	34 (4.0)	31 (3.7)NS
1998-2001	815 (35.1)	722 (88.6)	40 (4.9)	38 (4.7)	15 (1.8)	689 (84.5)	79 (9.7)	20 (2.5)	27 (3.3)	677 (83.1)	62 (7.6)	41 (5.0)	35 (4.3)	634 (77.8)	96 (11.8)	38 (4.7)	47 (5.8)
2002-2005	665 (28.6)	595 (89.5)	22 (3.3)	26 (3.9)	22 (3.3)	557 (83.8)	62 (9.3)	19 (2.9)	27 (4.1)	558 (83.9)	40 (6.0)	35 (5.3)	32 (4.8)	503 (75.6)	86 (12.9)	35 (5.3)	41 (6.2)

P values from Pearson's chi-squared test

§ p=0.02 * p=0.002 ‡ p=0.006 NS Not significant at 5%

§§ p=0.04 ** p=0.004 $ p=0.0001

Table S2: Mortality by comorbidity measures

Comorbidity	Mortality	
	One-year look-back period	Five-year look-back period
	HR (95%CI)[a]	HR (95%CI)[a]
Cervical cancer		
Charlson (1 unit)	1.28 (1.14-1.44)	1.21 (1.09-1.35)
Charlson 0	1.00[b]	1.00[b]
Charlson 1	1.41 (0.93-2.13)	1.17 (0.81-1.70)
Charlson 2	1.70 (1.14-2.55)	1.58 (1.09-2.30)
Charlson 3+	3.22 (1.73-5.99)	2.06 (1.25-3.42)
Elixhauser (1 unit)	1.25 (1.11-1.40)	1.18 (1.07-1.30)
Elixhauser 0	1.00[b]	1.00[b]
Elixhauser 1	1.29 (0.96-1.75)	1.29 (0.98-1.71)
Elixhauser 2	1.33 (0.83-2.13)	1.39 (0.92-2.10)
Elixhauser 3+	2.17 (1.32-3.56)	1.66 (1.07-2.60)
Other mortality (not cervical cancer)		
Charlson (1 unit)	1.64 (1.35-2.00)	1.69 (1.43-1.98)
Charlson 0	1.00[b]	1.00[b]
Charlson 1	1.35 (0.57-3.19)	2.65 (1.44-4.86)
Charlson 2	4.21 (2.08-8.51)	5.54 (2.85-10.78)
Charlson 3+	5.18 (1.57-17.04)	6.30 (2.71-14.65)
Elixhauser (1 unit)	1.46 (1.18-1.79)	1.64 (1.41-1.91)
Elixhauser 0	1.00[b]	1.00[b]
Elixhauser 1	2.49 (1.39-4.44)	2.51 (1.39-4.53)
Elixhauser 2	2.62 (1.20-5.72)	3.66 (1.80-7.44)
Elixhauser 3+	2.76 (1.04-7.30)	7.29 (3.71-14.29)
Total mortality		
Charlson (1 unit)	1.34 (1.21-1.48)	1.30 (1.19-1.42)
Charlson 0	1.00[b]	1.00[b]
Charlson 1	1.38 (0.95-2.01)	1.41 (1.03-1.94)
Charlson 2	2.10 (1.49-2.95)	2.01 (1.46-2.76)
Charlson 3+	3.40 (1.96-5.91)	2.49 (1.62-3.83)
Elixhauser (1 unit)	1.28 (1.15-1.41)	1.26 (1.16-1.36)
Elixhauser 0	1.00[b]	1.00[b]
Elixhauser 1	1.47 (1.13-1.92)	1.46 (1.14-1.87)
Elixhauser 2	1.48 (0.99-2.21)	1.66 (1.17-2.37)
Elixhauser 3+	2.20 (1.41-3.41)	2.23 (1.55-3.20)

[a] Adjusted for age, year of diagnosis, stage, ethnicity, NZDep, urban/rural residence

[b] Reference category

Table S3: Elixhauser comorbid conditions frequency and cervical cancer-specific mortality adjusted for individual comorbid conditions

Comorbidity	Frequency, n (%)		HR (95%CI)*	
	One-year look-back period	Five-year look-back period	One-year look-back period	Five-year look-back period
Congestive heart failure	33 (1.4)	51 (2.2)	2.35 (1.22-4.52)	1.76 (1.01-3.08)
Cardiac arrhythmia	35 (1.5)	54 (2.3)	1.38 (0.60-3.18)	1.08 (0.54-2.13)
Valvular disease	8 (0.3)	16 (0.7)	2.84 (0.70-11.61)	1.41 (0.35-5.71)
Pulmonary circulation disorders	6 (0.3)	12 (0.5)	-	1.54 (0.38-6.27)
Peripheral vascular disorders	14 (0.6)	25 (1.1)	1.15 (0.36-3.61)	0.98 (0.36-2.67)
Hypertension uncomplicated	104 (4.5)	143 (6.2)	0.98 (0.63-1.52)	1.02 (0.69-1.51)
Hypertension complicated	4 (0.2)	5 (0.2)	1.74 (0.24-12.72)	1.74 (0.24-12.72)
Paralysis	17 (0.7)	29 (1.3)	1.26 (0.40-3.99)	0.94 (0.39-2.30)
Other neurological disorders	20 (0.9)	31 (1.3)	1.22 (0.30-4.99)	1.30 (0.47-3.55)
Chronic pulmonary disease	56 (2.4)	96 (4.1)	1.62 (0.95-2.77)	1.34 (0.85-2.11)
Diabetes uncomplicated	57 (2.5)	70 (3.0)	2.17 (1.33-3.53)	2.07 (1.32-3.27)
Diabetes complicated	15 (0.7)	21 (0.9)	10.46 (3.01-36.37)	10.46 (3.01-36.37)
Hypothyroidism	12 (0.5)	18 (0.8)	0.31 (0.07-1.27)	0.41 (0.13-1.33)
Renal failure	27 (1.2)	32 (1.4)	4.27 (2.08-8.76)	3.71 (1.83-7.50)
Liver disease	13 (0.6)	21 (0.9)	2.43 (0.76-7.78)	1.39 (0.44-4.38)
Peptic ulcer disease excluding bleeding	3 (0.1)	6 (0.3)	-	-
AIDS/HIV	0	0	-	-
Lymphoma	2 (0.1)	4 (0.2)	0.90 (0.12-6.60)	1.03 (0.25-4.24)
Solid tumour without metastasis	66 (2.8)	93 (4.0)	1.15 (0.66-1.99)	1.12 (0.70-1.81)
Rheumatoid arthritis/collagen vascular diseases	7 (0.3)	13 (0.6)	1.15 (0.42-3.16)	1.25 (0.55-2.83)
Coagulopathy	9 (0.4)	11 (0.5)	2.78 (0.68-11.43)	3.61 (1.13-11.53)
Obesity	24 (1.0)	32 (1.4)	3.52 (1.55-7.98)	3.66 (1.79-7.46)
Weight loss	7 (0.3)	10 (0.4)	0.76 (0.10-5.57)	0.35 (0.05-2.56)
Fluid and electrolyte disorders	34 (1.5)	54 (2.3)	4.03 (2.01-8.08)	4.05 (2.25-7.26)
Blood loss anaemia	36 (1.6)	38 (1.6)	2.44 (1.48-4.00)	2.44 (1.50-3.96)
Deficiency anaemia	22 (1.0)	40 (1.7)	0.57 (0.21-1.55)	0.83 (0.41-1.69)
Alcohol abuse	8 (0.3)	24 (1.0)	1.23 (0.17-8.95)	0.43 (0.10-1.82)
Drug abuse	4 (0.2)	10 (0.4)	3.28 (0.45-23.76)	4.94 (1.21-20.17)
Psychoses	7 (0.3)	21 (0.9)	0.70 (0.10-5.01)	1.51 (0.56-4.10)
Depression	9 (0.4)	28 (1.2)	1.01 (0.25-4.09)	1.43 (0.63-3.25)

* Adjusted for age, year of diagnosis, stage, ethnicity, NZDep, and urban/rural residence
For the hazard ratio estimate for each comorbidity the reference group is women that do not have that comorbidity.

Table S4: Cervical cancer-specific mortality by ethnicity adjusted for comorbidity with one-year look-back period

Comorbidity	Comorbidity	Ethnicity			
		Other	Māori	Pacific	Asian
	HR (95%CI)[a]	HR (95%CI)[b]	HR (95%CI)[c]	HR (95%CI)[c]	HR (95%CI)[c]
No comorbidity adjustment/inclusion		1.00	1.56 (1.19-2.05)	1.95 (1.21-3.13)	0.72 (0.41-1.27)
Indices as continuous variable					
Charlson	1.28 (1.14-1.44)	1.00	1.57 (1.20-2.06)	1.85 (1.15-2.97)	0.73 (0.42-1.30)
Elixhauser	1.25 (1.11-1.40)	1.00	1.55 (1.19-2.04)	1.92 (1.20-3.09)	0.72 (0.41-1.26)
Individual comorbid conditions					
Congestive heart failure	2.35 (1.22-4.52)	1.00	1.57 (1.20-2.06)	1.98 (1.23-3.17)	0.72 (0.41-1.27)
Valvular disease	2.84 (0.70-11.61)	1.00	1.56 (1.19-2.04)	1.96 (1.22-3.14)	0.72 (0.41-1.27)
Hypertension, complicated	1.74 (0.24-12.72)	1.00	1.57 (1.19-2.06)	1.95 (1.22-3.13)	0.72 (0.41-1.27)
Chronic pulmonary disease	1.62 (0.95-2.77)	1.00	1.55 (1.18-2.03)	1.95 (1.22-3.13)	0.67 (0.38-1.19)
Diabetes, complicated	10.46 (3.01-36.37)	1.00	1.55 (1.18-2.04)	1.70 (1.03-2.80)	0.71 (0.40-1.25)
Renal failure	4.27 (2.08-8.76)	1.00	1.58 (1.20-2.07)	1.70 (1.04-2.77)	0.72 (0.41-1.27)
Liver disease	2.43 (0.76-7.78)	1.00	1.55 (1.18-2.03)	1.92 (1.20-3.09)	0.72 (0.41-1.26)
Coagulopathy	2.78 (0.68-11.43)	1.00	1.55 (1.18-2.03)	1.91 (1.19-3.07)	0.72 (0.41-1.27)
Obesity	3.52 (1.55-7.98)	1.00	1.55 (1.18-2.04)	1.90 (1.18-3.05)	0.72 (0.41-1.27)
Fluid and electrolyte disorders	4.03 (2.01-8.08)	1.00	1.51 (1.15-1.98)	1.97 (1.23-3.16)	0.69 (0.39-1.21)
Blood loss anaemia	2.44 (1.48-4.00)	1.00	1.53 (1.17-2.01)	1.98 (1.23-3.17)	0.71 (0.40-1.26)
Drug abuse	3.28 (0.45-23.76)	1.00	1.56 (1.19-2.04)	1.95 (1.22-3.13)	0.72 (0.41-1.27)
All 12 of the above		1.00	1.44 (1.09-1.89)	1.62 (0.98-2.68)	0.63 (0.35-1.13)

[a] Adjusted for age, year of diagnosis, stage, ethnicity, NZDep, urban/rural residence

[b] Reference category

[c] Adjusted for age, year of diagnosis, stage, ethnicity, NZDep, urban/rural residence and comorbidity index

APPENDIX 5

Statement of contribution for “Travel time and distance to healthcare”

MASSEY UNIVERSITY
GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION TO DOCTORAL THESIS CONTAINING PUBLICATIONS

(To appear at the end of each thesis chapter/section/appendix submitted as an article/paper or collected as an appendix at the end of the thesis)

We, the candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of Candidate: NAOMI BREWER

Name/Title of Principal Supervisor: ASSOCIATE PROFESSOR BARRY BORMAN

Name of Published Research Output and full reference: Travel time and distance to health care only partially account for the ethnic inequalities in cervical cancer stage at diagnosis and mortality in New Zealand. Australian and New Zealand Journal of Public Health 2011; in press

In which Chapter is the Published Work: CHAPTER FIVE

Please indicate either:

- **The percentage of the Published Work that was contributed by the candidate:** 85%.
  and / or
- **Describe the contribution that the candidate has made to the Published Work:**

A Brewer
Candidate's Signature

2/11/11
Date

Principal Supervisor's signature

2/11/11
Date

APPENDIX 6

Statement of contribution for “Ethnic inequalities in cervical cancer survival in NZ”

MASSEY UNIVERSITY
GRADUATE RESEARCH SCHOOL

STATEMENT OF CONTRIBUTION TO DOCTORAL THESIS CONTAINING PUBLICATIONS

(To appear at the end of each thesis chapter/section/appendix submitted as an article/paper or collected as an appendix at the end of the thesis)

We, the candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated below in the *Statement of Originality*.

Name of Candidate: NAOMI BREWER

Name/Title of Principal Supervisor: ASSOCIATE PROFESSOR BARRY BORMAN

Name of Published Research Output and full reference: Which factors account for the ethnic inequalities in stage at diagnosis and cervical cancer survival in New Zealand? Submitted for publication

In which Chapter is the Published Work: CHAPTER SIX

Please indicate either:

- **The percentage of the Published Work that was contributed by the candidate:** 85%.
  and / or
- **Describe the contribution that the candidate has made to the Published Work:**

NBrewer
Candidate's Signature

2/11/11
Date

Principal Supervisor's signature

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