



A population-based examination of cancer in
New South Wales farm residents
compared to rural non-farm and urban residents.

Julie Catherine Depczynski

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Faculty of Medicine, School of Public Health, The University of Sydney*

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Abbreviations

ABS	Australian Bureau of Statistics
ACR	Australian Coordinating Registry
AgW	Agricultural worker
AIHW	Australian Institute of Health and Welfare
APDC	Admitted Patients Data Collection
APVMA	Australian Pesticide and Veterinary Medicines Association
ARIA+	Accessibility/Remoteness Index of Australia (plus)
ASGS	Australian Statistical Geography Standard
CASP	Critical Appraisal Skills Program
CHeReL	Centre for Health Record Linkage
CI	Confidence Interval
CL	Confidence Limit
COD URF	Cause of Death Unit Record File
EPHPP	Effective Public Health Practice Project
FOBT	Faecal Occult Blood Test
GP	General medical Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HPV DNA	Human Papillomavirus Deoxyribonucleic Acid
HR	Hazard ratio
HREC	Human Research Ethics Committee
ICD	International Statistical Classification of Diseases
ICD-10-AM	International Statistical Classification of Diseases Tenth Revision -Australian Modification
MBS	Medicare Benefits Schedule
MLK	Master Linkage Key
NCSC	National Cancer Statistics Clearing House
NHL	non-Hodgkin Lymphoma
NMSC	non-melanoma skin cancers
NSW	New South Wales
NSW CR	New South Wales Cancer Registry
OR	Odds Ratio
PHSREC	Population and Health Services Research Ethics Committee
PPN	Project Person Number
PSA	Prostate Specific Antigen
PTR	Pap Test Register
RBDM	Register of Births, Deaths and Marriages
RR	Risk Ratio
rSMR	Relative Standardised Mortality Ratio
SAS 9.3™	Statistical Analysis Software Version 9.3 (Trademark)
SEIFA	Socio-Economic Indexes for Areas
SIR	Standardised Incidence Rate or Ratio
SMR	Standardised Mortality Rate or Ratio
STROBE	Strengthening of reporting of observational studies in epidemiology statement
SURE	Secure Unified Research Environment
UFW	United Farmworkers of America

Disclosure

This thesis is submitted to the University of Sydney in fulfillment of the requirements for the Degree of Doctor of Philosophy.

The work presented is a hybrid of a traditionally structured thesis, with introduction, literature review, methods and discussion chapters; complimented by a series of published and unpublished manuscripts which form part of the literature review and the results section.

All information obtained from other sources is acknowledged and referenced as appropriate. The research is an original contribution, which has been compiled under the primary supervision of Associate Professor Tony Lower from the Australian Centre for Agricultural Health and Safety, Sydney School of Public Health, The University of Sydney. My co-supervisors have been (1) Emeritus Professor Bruce Armstrong, Sydney School of Public Health, The University of Sydney and Adjunct Professor, School of Population Health, University of Western Australia; and (2) Professor Timothy Dobbins, National Drug and Alcohol Research Centre, University of New South Wales. Specific contributions to jointly authored papers are outlined in the following section.

I hereby declare I have not submitted this material, in either full or in part, for a degree at this or any other institution.

Signature _____ Date _____

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Short abstract

The cancer indicators and outcomes of rural Australians are generally less favourable than those of their urban counterparts, but the situation for farm residents is less well known. With a focus on farm residents, this study aimed to identify differences between farm, rural non-farm and urban residents in a large NSW cohort, in: (1) incidence and mortality from major cancers; (2) screening rates, stage at diagnosis and selected cancer therapies; and (3) common risk factors associated with these cancers.

Cancers of interest were breast, cervical, colorectal, lung and prostate cancers; melanoma and Non Hodgkins Lymphoma. The Sax Institute's 45 and Up Study was used to define resident groups and to compare baseline cancer-related risk factors. Cancer mortality, incidence, stage at diagnoses, cancer screening practices and selected cancer treatments were compared through data linkage with routine state and national health datasets. Direct age-standardisation, proportional hazards regression and logistic regression were used to compare cancer indicators, controlling for common risk factors.

Overall, farm residents had lower all cancer incidence and mortality risk than rural non-farm or urban counterparts, but differences were only significant for all cancer incidence in farm women compared to rural non-farm women. For specific cancers, breast cancer mortality risk was also significantly lower in farm women than rural non-farm women, but incidence and mortality risk for other cancers were not significantly different. However, whilst confidence intervals did not exclude unity, adjusted point estimates for incidence or mortality risk suggest that compared to other groups, farm residents had a similar or reduced risk of breast, colorectal and lung cancer; similar risk of NHL; and farm men similar or slightly raised risk of melanoma and prostate cancer. There were no significant differences in stage at diagnosis for prostate, breast and colorectal cancers. Small case numbers in the farm group were likely to have contributed to lack of significance of findings for some analyses.

Screening practices of farm and rural non-farm residents were generally similar; but both rural groups had significantly less frequent PSA tests, Pap tests, mammograms and colonoscopies than urban residents. Cancer-related surgical services for breast and colorectal cancer were comparable between all groups. Some findings for non-surgical therapies should be considered with caution, but both farm and rural non-farm residents were significantly less likely to access chemotherapy for breast cancer and brachytherapy for prostate cancer than urban counterparts.

Strengths and limitations of the research are discussed. Pending confirmation of findings in other studies, results have implications for cancer screening and treatment services in rural Australia. The reasons why farm residents may have lower incidence and / or mortality risk for some cancers should also be considered for further research.

Long abstract

Chapter 1:

This chapter provides an introduction and background to the study, leading toward a statement of the research objectives. It begins with a brief summary of the impact of cancer, which is responsible for approximately one third of all deaths in Australia. As a category of disease, cancer can inflict sufferers with months or years of debilitating illness and complex treatment regimes. Societal impacts include health system costs, lost productivity and a considerable burden of disease. The most expensive cancers to society in Australia are lung, colorectal and breast cancers. The most commonly diagnosed cancers are prostate, colorectal and breast cancer, whilst lung, colorectal, prostate and breast cancer account for most deaths. However, overall death rates from cancer have declined in recent years, largely attributed to improvements in screening, diagnosis, treatment and survival outcomes for certain cancers.

Health reports suggest that the incidence and mortality of several major cancers tend to be higher amongst the one-third of Australians residing outside major cities. Although there is no simple gradient of increasing cancer with increasing remoteness, people in major cities do tend to be the healthier for most cancer indicators. Rural Australians have been reported to have higher levels of smoking and alcohol use; an older demographic profile; a higher proportion of indigenous people; and education, employment and socio-economic disadvantage, which may contribute to poorer health and/or cancer indicators in rural areas. Geographic distance from services may also play a role. It is possible distance could impact on decisions regarding the types of medical treatment received, including referral to specialist cancer centres.

Within rural Australia, there are approximately 93,000 farm families; one third of whom are located in NSW. People who live and /or work on farms have unique characteristics regarding employment,

lifestyle, potential environmental exposures and socio-economic factors; and constitute a sizeable rural population for which there is very limited information about cancer indicators and risk factors. Only two previous studies have been published on cancer risk in Australian farmers, suggesting the possibility of higher incidence or mortality from lymphohaematopoietic and prostate cancer. It is not known if farm exposures or differences in other risk factors may have contributed to this, or whether there are any differences in other cancers between farm residents and others, controlling for common risk factors.

Focusing on farm residents, this study aims to identify if variations exist between farm, non-farm rural and urban residents in a large NSW cohort, in relation to: (1) incidence and mortality from selected major cancers; (2) screening rates, stage at diagnosis and selected cancer therapies; and (3) differences between groups in common risk factors associated with these cancers. There was also a secondary interest in whether rural groups differed from the urban group - particularly in relation to baseline risk factors and health service related indicators. A series of studies examine these issues, adding to the body of evidence on cancer risk in rural areas and identify potential disadvantage. Strengthening the evidence base on which health policy and resourcing decisions are potentially made, is an important role of epidemiological and health services research.

Chapter 2

The objectives of the literature review were to examine the evidence for differences between farmers and non-farmers in the incidence, mortality, screening, stage at diagnosis, treatment and survival outcomes for 'all cancers' and selected major cancers. Eligibility criteria were developed to guide selection of appropriate studies; and retrieval and quality assessment methods described. A set of summaries was developed, focusing on particular elements or cancers. The first was an overview of previous reviews of cancer incidence and mortality in farmers. Further summaries are based on primary studies relating to: (1) comparative cancer mortality/incidence; (2) a review focusing on prostate cancer

incidence and mortality in farmers published in a peer-reviewed journal; and (3) a summary of health service related studies comparing farm and non-farm groups.

The evidence on cancer risk in farmers compared to non-farmers from previous reviews is suggestive of a deficit for all cancer, bladder, colorectal and lung cancers. An excess of risk in farmers was suggested for lip, prostate, some lymphohaematopoietic cancers and possibly brain cancers. However, the strength of evidence for excess or deficit of different cancers in farmers is relatively weak due to the low volume of studies for each cancer type; and inconsistent methodological approaches which make comparisons difficult.

Our current review of primary studies published since 2002 also suggested farm groups had lower all cancer and lung cancer risk; and a deficit in colorectal cancer. Slightly reduced or neutral risk of breast cancer was suggested and neutral risk of melanoma. A neutral to excess risk was suggested for some lymphohaematopoietic cancers. Generally, the evidence for excess cancer risk in farm groups in our review was perhaps weaker than in previous, older reviews. Similar to previous reviews, however, there were limitations in the strength of conclusions which could be drawn, for methodological reasons.

Prostate cancer risk was of particular interest due to an earlier report of elevated mortality risk in Australian farmers. A review focusing on prostate cancer risk in farmers was published in an international peer reviewed journal in 2014 (*Cancer Epidemiology*). Eighteen primary research articles were assessed. Four of ten mortality studies and two of nine incidence studies reported statistically significant increases in prostate cancer risk in farmers. However, nearly half of all studies reported non-significant reductions in farmers' risk. Additionally, one study reported significantly increased and decreased risk using different outcome measures. Results varied considerably by geographic region, study design and degree of control for confounders, affecting comparability and strength of findings. As for other cancers, the overall evidence for increased prostate cancer risk in farmers was weak.

Given the geographic dispersion of rural Australia, there is potential for health service related factors to have a considerable impact on cancer identification and treatment. A summary of findings was presented for stage at diagnosis and treatment; cancer survival and cancer screening between farmers and non-farmers. Whilst component studies were of reasonable quality, the volume and level of evidence on differences between farmers and others was generally low or insufficient. One of the objectives of the primary research project is to address this gap in knowledge by comprehensively assessing the epidemiology of cancer and comparative health service usage in NSW farm residents compared to others.

Chapter 3

This Chapter provides an overview of the study methods, including background information on the 45 and Up Study; methods used to prepare the data for analyses; and a description of analytical methods. This was a large cohort study of mixed prospective and retrospective design, providing primary analysis of baseline survey data as well as follow-up analysis of secondary linked data. The 45 and Up Study cohort was the primary dataset of interest and formed the basis for derivation and comparison of (a) farm residents; (b) non-farm rural residents; and (c) urban participants for a range of cancer and health-related variables. The sub-group of interest comprised those who stated they lived in a 'house on farm' in the 45 and up Study baseline questionnaire.

The 45 and Up Study is managed by the Sax Institute in collaboration with major health agency partners, as listed within the 'acknowledgements'. Eligible individuals were randomly sampled from the enrolment database of the Australian Department of Human Services (formerly Medicare Australia), which provides near complete coverage of the NSW population. Persons aged 45 and over and resident in NSW were invited to take part between January 2006 and December 2009. The overall response rate (17-18%) is comparable with other large cohort studies, although not truly representative of the general

NSW population. However, with over 267,000 participants, the cohort approximated 11% of the NSW population aged 45 years and over in 2009.

Cancers of interest for different components of the research were breast, cervical, colorectal, lung and prostate cancers as well as melanoma and Non Hodgkins Lymphoma. Firstly, a comparison of self-reported personal and behavioural risk factors of interest, as recorded on the 45 and Up Study baseline questionnaire, was completed. Secondly, a comparison of cancer mortality, incidence, stage at diagnoses, cancer screening practices and selected cancer treatments was made; by linking data from the 45 and Up Study participant records with matching records from routine state and national health datasets.

Secondary datasets used for the different component studies were the Australian Coordinating Registry (ACR) Cause of Death Unit Record File (COD URF), Medicare Benefits Schedule (MBS), NSW Admitted Patients Data Collection (APDC), NSW Cancer Registry (NSW CR), NSW Pap Test Register (PTR) and the NSW Register of Births, Deaths and Marriages (RBDM). Characteristics of each data dataset, data linkage processes and quality assurance processes are described.

Derivation of the cohort variable was of particular importance. 'Farm residents' were defined as those who indicated that they lived in a 'house on farm' on the 45 and Up Study baseline questionnaire. Rural 'non-farm' and urban residents were further defined by ARIA+/ ASGS category. Participants who did not live in a house on a farm whose ARIA+/ ASGS classification indicated they did not live in a 'Major city', were defined as rural non-farm residents. The remaining group of 'urban residents' were those who specified that they lived in a 'Major City'.

Methods of analysis for each component of the study are described. Analyses were conducted within SAS 9.3 and Microsoft Excel TM and included summary statistics of sub-group characteristics; derivation of direct age-standardised cancer incidence and mortality rates and ratios; use of proportional hazard regression to determine hazard ratios for selected cancers, controlling for

commonly known confounders; and logistic regression to compare cancer stage at diagnosis between sub-groups, MBS claims-based cancer screening frequency and cancer treatments in the NSW APDC. The following chapters reiterate some of the above information, to fulfill requirements of stand-alone manuscripts submitted for publication. In particular, more detail on analytical methods undertaken as they pertain to specific study components, is provided.

Chapter 4

This component study forms a standalone manuscript prepared for submission to a peer reviewed journal. The study addresses the first and third objectives of the overall research project. That is, to identify if variations exist between farm, non-farm rural and urban residents in the cohort, in relation to (1) mortality from selected major cancers; and (2) differences between groups in common risk factors associated with these cancers. This is important, to determine whether farm residents (or other groups) are disadvantaged regarding cancer health indicators and /or mortality, which may have implications for targeting of health services. The manuscript is entitled: *'Cancer risk factors and mortality in farm, rural non-farm and urban residents within the 45 and Up Study cohort.'* The abstract submitted with this manuscript is provided below.

Introduction: People living in rural areas in Australia have poorer cancer outcomes than those in urban areas, but it is not known if this is the case for farm residents. **Methods:** Data for farm, rural non-farm and urban participants of the 45 and Up Study cohort in New South Wales, Australia, were linked with state death registrations data for 2006 - 2012. Direct age-standardised mortality rate ratios for 267,074 participants were compared for all cancer and prostate, breast, lung and colorectal cancers, non-Hodgkins Lymphoma (NHL) and melanoma. Proportional hazards regression was used to estimate adjusted mortality hazard ratios for each cancer type, controlling for common risk factors. **Results:** Farm, rural non-farm and urban residents differed in a range of health related characteristics. Farm women had a significantly lower adjusted hazard ratio for breast cancer than rural non-farm women.

Confidence intervals for adjusted hazard of all cancer and other selected cancers did not exclude unity, but point estimates suggested farm residents had non-significantly lower all cancer and colorectal cancer mortality risk; similar lung cancer risk; and farm men slightly elevated melanoma and prostate cancer risk. **Conclusion:** Farm women had a significantly lower breast cancer mortality risk than rural non-farm women, but differences between farm, rural non-farm and urban residents for all cancer or other selected cancers were not significant.

Chapter 5

This study was submitted as a standalone manuscript to an international peer reviewed journal in October 2016 (*BMC Cancer*). The study addresses the first objective of the overall research project, to identify if variations exist between farm, non-farm rural and urban residents in the cohort in relation to incidence of selected major cancers. Similar to the previous chapter, this is important, to identify whether farm residents (or other groups) are disadvantaged regarding cancer incidence, which may have implications to health services providing screening and treatment services. The manuscript is entitled: '*Cancer incidence in farm, rural non-farm and urban residents in the 45 and Up Study cohort, New South Wales, Australia.*' The abstract submitted with this manuscript is provided below.

Background: It is not known if the incidence of common cancers in Australian farm residents is different to rural non-farm or urban residents. **Methods:** Data from farm, rural non-farm and urban participants of the 45 and Up Study cohort in New South Wales Australia, were linked with state cancer registry data for the years 2006 - 2009. Direct age-standardised incidence rate ratios were compared for all cancer, prostate, breast, colorectal cancer, melanoma and non-Hodgkin lymphoma (NHL). Proportional Hazards regression was used to generate incidence hazard ratios for each cancer type adjusted for relevant confounders. **Results:** Farm women had a significantly lower all cancer hazard ratio than for rural non-farm women; but lower all cancer risk in farm men compared to rural non-farm and urban counterparts was not significant. When rural non-farm and urban groups were combined, the

all cancer adjusted hazard was significantly lower in both farm men and women. Confidence intervals did not exclude unity for differences in risk of prostate, breast, colorectal or lung cancers, NHL or melanoma, but farm residents had considerably lower lung cancer risk than other residents after controlling for smoking and other factors. **Conclusions:** All cancer risk was significantly lower in farm residents compared to combined rural non-farm and urban groups. Farm women also had a significantly lower all cancer adjusted hazard ratio than rural non-farm women. These differences appeared to be mainly due to lower lung cancer incidence rates in farm residents.

Chapter 6

This component study was submitted as a standalone manuscript to an Australian peer reviewed journal in December 2016 (*Australian Journal of Rural Health*). The manuscript addresses the second objective of the overall research project, to identify if variations exist between farm, non-farm rural and urban residents in the cohort, in relation to stage at diagnosis of prostate, breast and colorectal cancers. Again, this is important, to identify whether farm residents (or other groups), are disadvantaged regarding diagnosis and early identification of major cancers, which may have implications for primary health services including general medical practices, screening and diagnostic services. The manuscript is entitled: '*Stage of diagnosis of prostate, breast and colorectal cancer in farm residents compared to other rural and urban residents in New South Wales.*' The abstract submitted with this manuscript, is formatted to the Australian journal's requirements.

Objective: To determine if stage at diagnosis of prostate, breast and colorectal cancers differs between farm, rural non-farm and urban residents. **Design:** Data-linkage of baseline survey information from a large cohort study, with state cancer registry records from 2006-2009. **Setting:** New South Wales (NSW), Australia. **Participants:** NSW residents enrolled in the 45 and Up Study cohort. **Main outcome measures:** Adjusted Odds Ratio of non-localised cancer stage was modelled using binary logistic regression, controlling for commonly known cancer risk factors. **Results:** Overall differences in the

odds ratios for later stage prostate, breast and colorectal cancer diagnosis in farm men and women compared to either rural non-farm or to urban counterparts, were not statistically significant; although farm men had twice the odds of either group of being diagnosed at later stage colorectal cancer. The odds of later stage prostate cancer for farm and urban men were similar, but rural non-farm men were significantly less likely than urban men to be diagnosed at later stage. Higher household income was associated with later stage breast and prostate cancer; and private health insurance with extras negatively associated with later stage prostate cancer. **Conclusions:** Differences in stage of cancer diagnosis, particularly farm and rural non-farm men remain unexplained but were not statistically significant. Farm men may be at higher risk of later stage colorectal cancer diagnosis, which if confirmed has implications for research on possible reasons; and for the delivery of appropriate cancer diagnostic services in rural areas.

Chapter 7

This study forms a standalone manuscript submitted to an international peer reviewed journal in March 2017 (*BMC Public Health*). It also addresses the second objective of the overall research project; in this case to identify if variations exist between farm, non-farm rural and urban residents in the cohort in relation to screening for prostate, breast, colorectal and cervical cancers. This is important, to identify whether farm residents (or other groups) are disadvantaged regarding utilisation of screening services, which may impact upon the timely identification of screenable cancers. It may have implications for population-wide screening programs (e.g. Bowelscreen, Breastscreen); and other services that provide screening or diagnostic testing (general practices, Area Health Services, pathology services). The manuscript is entitled: '*Cancer screening practices in a cohort of Australian farm, rural non-farm and urban residents aged 45 years and over.*' The abstract for this manuscript is provided below in international journal format.

Background: Screening for breast, prostate, colorectal and cervical cancers can lead to earlier diagnosis and more effective treatment, but it is not known if cancer screening practices of farm residents in Australia differ from their rural or urban counterparts. **Methods:** Self-reported screening for prostate, breast and colorectal cancer were compared for farm, rural non-farm and urban participants of the 45 and Up Study cohort in New South Wales (NSW). Data for participants under 75 years of age and without prior cancer, were linked with NSW Pap Test Register records for cervical screening frequency from 2006-2012. Records were also linked with Medicare Benefits Schedule claims data for 2004-2011 for visits to a General medical Practitioner (GP); and for breast, prostate and colorectal screening procedures. Age-adjusted comparisons were made using general linear regression and logistic regression. **Results:** Farm residents were significantly less likely to visit a GP, but screening practices between farm and rural non-farm residents were generally similar. Urban residents had significantly more prostate specific antigen (PSA) tests, Pap tests, mammograms and colonoscopies than either of the other groups. Urban residents were also significantly more likely to report ever having a mammogram or colonoscopy. In contrast, farm and rural non-farm residents had significantly more Faecal Occult Blood Tests (FOBTs) than urban counterparts; and were around one third more likely than urban residents to report ever having a FOBT. Farm residents were most likely to report ever having a PSA test or 'any' form of colorectal screening test, with both rural groups significantly more likely to do so than urban residents. **Conclusions:** Farm and rural non-farm residents had lower utilisation and perhaps reduced access to specialist or procedural screening services.

Chapter 8

This final component study forms a standalone manuscript prepared for submission to an Australian peer reviewed journal. The study addresses the second objective of the overall research project; to identify if variations exist between farm, non-farm rural and urban residents in the cohort, in relation to selected treatments for prostate, breast and colorectal cancers. This is important, to identify whether

farm residents (or other groups) are disadvantaged regarding access or utilisation of different cancer therapies. This potentially has implications for general practices, Area Health Services and pathology services, which need to co-ordinate to provide optimal care. It may also provide baseline data for recently established Rural Cancer Centres and cancer networks, which have a base against which to measure improvements over time. The manuscript is entitled: *'A comparison of cancer therapies in a cohort of farm, rural non-farm and urban residents aged 45 years and over in New South Wales.'* The abstract for this manuscript is provided below, in Australian journal format.

Objectives: To determine if selected therapies for prostate, breast and colorectal cancer vary by farm, rural non-farm or urban residence. **Design:** Data linkage of baseline survey information from the Sax Institutes' 45 and Up Study cohort with data from the New South Wales (NSW) Admitted Patients Data Collection (APDC) for 2006-2012. **Setting:** NSW. **Participants:** Farm, rural non-farm and urban residents aged 45 years and over. **Main outcome measures:** Surgical, chemotherapy, radiotherapy and brachytherapy procedures for those with a diagnosis of prostate, breast or colorectal cancer. Average distance to treating hospital and the odds of receiving selected therapies for each cancer was compared, controlling for selected variables. **Results:** Farm men were significantly more likely to have a prostatectomy for prostate cancer than rural non-farm men, but differences for breast and colorectal cancer surgery between resident groups were not significant. Farm and rural non-farm men had significantly lower odds of having brachytherapy for prostate cancer than urban men; and farm and rural non-farm women were significantly less likely to have chemotherapy for breast cancer than urban women. Rural non-farm residents were also significantly less likely to have chemotherapy for colorectal cancer than urban counterparts. Age, distance, income and health insurance factors contributed to differences in non-surgical care between groups. **Conclusion:** Cancer-related surgical services for breast and colorectal cancer were generally comparable between groups. Farm and rural non-farm residents may have been disadvantaged in relation to non-surgical therapies for prostate, breast and colorectal cancer compared to urban residents.

Chapter 9

The central aim of this body of work was to examine and compare cancer indicators in Australian farm residents compared to non-farm rural and urban residents. Information on the comparative cancer profile of Australian farm residents will contribute to the evidence base on which rural health policy and resourcing decisions are potentially made. Farmers and farm families have particular characteristics regarding their age profile, employment, lifestyle, potential environmental exposures and socio-economic conditions. This raises questions as to whether farmers have a different cancer profile to other rural or urban people, despite being part of the larger rural and state populations.

An overview of cancer in rural Australia provided context to the research. Generally, urban residents had lower cancer incidence and mortality than rural people. A range of socio-demographic characteristics have been suggested in influencing cancer indicators. Geographic distance from services may also contribute to delays in diagnosis and decisions regarding cancer treatment. Given limited Australian studies of cancer risk in farmers, a review of the international literature was undertaken. Overall deficits in all cancer, lung and colorectal cancer risk were suggested; and a deficit or neutral risk of breast cancer and neutral risk of melanoma. Mainly neutral but some excess risk was suggested for some lymphohaematopoietic cancers. Compared to earlier reports of higher prostate cancer risk in farmers in Australia, the overall evidence for elevated prostate cancer risk in farmers in the literature review was weak, partly due to disparate study methods. There was also insufficient evidence on differences in cancer screening, stage at diagnosis or treatment between farm and non-farm groups in the literature.

Prior to this study, information on cancer indicators in Australian farm residents was extremely limited. A series of component studies were undertaken to examine differences between NSW farm, non-farm rural and urban residents in cancer incidence or mortality; stage of diagnosis, screening and selected cancer therapies; and of common risk factors that might be associated with these cancers. The

45 and Up Study cohort enabled identification of farm residents, not otherwise identifiable in standard population-wide health reports. Comparison of cancer indicators between groups was made possible through data linkage to administrative health datasets.

Farm, rural non-farm and urban residents in the cohort differed in age and a range of characteristics, which were controlled for in multivariate regression models. Findings were generally consistent with those of the review. Overall, farm residents had lower all cancer incidence and mortality risk than rural non-farm or urban residents but differences were only significant for all cancer incidence in farm women compared to rural non-farm women. For specific cancers, breast cancer mortality risk was significantly lower in farm women than rural non-farm women, but differences for other cancers were not significant. Of these, farm residents had similar or reduced point estimates for breast, colorectal and lung cancer risk; similar risk of NHL; and farm men had similar or slightly raised risk of melanoma and prostate cancer. Small case numbers in the farm group were likely to have contributed to lack of significance of findings for some analyses.

There were no significant differences in stage at diagnosis for prostate, breast and colorectal cancers; although the higher odds for later colorectal cancer in farm men warrants further investigation. Screening practices of farm and rural non-farm residents were similar, but results suggested that compared to urban residents, both rural groups had lower utilisation and perhaps reduced access to screening services. In general, cancer-related surgical services for breast and colorectal cancer were also comparable between groups. Whilst findings for chemotherapy and radiotherapy should be considered with caution due to data limitations, these suggest farm and rural non-farm residents may have been disadvantaged regarding non-surgical therapies for prostate, breast and colorectal cancer. This is consistent with findings of other studies on rural versus urban cancer services in Australia.

Comparisons across several indicators for a particular cancer type can also assist in identifying patterns that may have implications for rural health services and resource allocation. Whilst

acknowledging that most differences between groups were not statistically significant, an exploratory discussion was undertaken on indicators across cancer types, raising questions for further consideration. However, suggested inferences need to be confirmed with greater case numbers over longer periods of time; and within other cohorts.

Strengths of this research are discussed, including the robust sampling methods of the original 45 and Up Study, the ability to identify farm residents in the cohort, the inclusion of cancer indicators in farm women, the ability to capture health system interactions through data linkage for a range of cancer-related indicators; and the ability to repeat these analyses over a longer period of time, to reassess findings.

Limitations discussed include the level of representativeness of the NSW population. Importantly, small case numbers in the farm group have resulted in low power for some analyses contributing to wide confidence intervals and a bias toward insignificant findings. A cautious or conservative interpretation of findings is warranted. Some of these factors could be addressed with longer follow-up time. There were also inherent limitations in defining or interpreting what constitutes a farm resident, which may have contributed to a bias toward the null.

A number of questions arise from the research. If confirmed by other studies, there is a need to address the suggested: (1) higher risk of later stage diagnosis of colorectal cancer in farm men; (2) lower rates of brachytherapy, chemotherapy and combined therapies for prostate cancer in farm men; and (3) wider rural disadvantage in non-surgical cancer treatments for prostate, colorectal and breast cancers and perhaps lung cancer. Furthermore, investigation of the possible reasons why farm residents might have generally better incidence and / or mortality profiles for breast, colorectal and lung cancers, could inform ways to reduce the impact of these cancers upon individuals and wider communities. Addressing these questions will contribute to a greater understanding of the epidemiology of cancer in Australian farm residents and the wider rural community.

Publications arising out of thesis

1. Depczynski J, Lower T. **A review of prostate cancer incidence and mortality studies of farmers and non-farmers, 2002-2013.** *Cancer Epidemiology* 2014, 38(6):654-662.
2. Depczynski J, Dobbins T, Armstrong B, Lower T. **Cancer risk factors and mortality in farm, rural non-farm and urban residents within the 45 and Up Study cohort.** Manuscript prepared for peer review journal.
3. Depczynski J, Dobbins T, Armstrong B, Lower T. **Cancer incidence in farm, rural non-farm and urban residents in the 45 and Up Study cohort, New South Wales, Australia.** *BMC Cancer* Manuscript awaiting review. October 2016.
4. Depczynski J, Dobbins T, Armstrong B, Lower T. **Stage at diagnosis of prostate, breast and colorectal cancer in farm residents compared to other rural and urban residents in New South Wales.** *Australian Journal of Rural Health*. Manuscript under review December 2016
5. Depczynski J, Dobbins T, Armstrong B, Lower T. **Cancer screening practices in a cohort of Australian farm, rural non-farm and urban residents aged 45 years and over.** *BMC Public Health*. Manuscript awaiting review. March 2017.
6. Depczynski J, Dobbins T, Armstrong B, Lower T. Armstrong B. **A comparison of cancer therapies in a cohort of Australian farm, rural non-farm and urban residents aged 45 years and over.** Manuscript prepared for peer review journal.

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Abstracts presented

1. Depczynski J, Lower T. *Cancer in farmers: An international review*. NSW Rural & Remote Health Congress. Wagga Wagga 5-6 November 2012.
2. Depczynski J, Lower T. *Remote access to big datasets – enabling rural-based research on cancer in NSW farmers*, NSW Rural Health and Research Congress, Port Macquarie 21-23 October 2013
3. Depczynski J, Lower T. *Cancer in farmers, non-farm rural and urban residents in the NSW '45 and Up' Study*. NSW Rural Health & Research Congress, Dubbo, 9-10 September 2014
4. Depczynski J, Lower T. *Cancer in farmers, non-farm rural and urban residents in the NSW '45 and Up' Study cohort*. 10th National Farm Health & Safety Conference Launceston, 15 -16 October 2014
5. Depczynski J, Lower T. *Cancer in farmers, non-farm rural and urban residents in the NSW '45 and up' study cohort*, 2014 Postgraduate Cancer Research Symposium, The University of Sydney, 3 November 2014

Author contribution statements for publications (one to six)

Contribution statements for each of the six papers prepared for publication as part of this body of work are provided on the following pages. Signed versions are retained by The University of Sydney.

Statement of contribution to publication

Dear co-author,

Re: Depczynski J, Lower T. A review of prostate cancer incidence and mortality studies of farmers and non-farmers, 2002-2013. *Cancer Epidemiology* 2014, 38(6):654-662.

I would like to use the above paper as a chapter in my PhD thesis and request your permission to do so. It is a requirement of the Academic Board of the University of Sydney, that a signed statement is obtained from all co-authors attesting to my contribution to this paper as evidence to satisfactorily identify the sections of the work for which I was responsible.

Author contributions

Julie Depczynski conceived, designed and conducted the literature review, interpreted the findings and drafted and revised the manuscript. Tony Lower interpreted the findings and critically reviewed and revised the manuscript.

If you agree with the contributions outlined above and give permission for this paper to be part of my PhD thesis, please sign below. Thank you for your contribution and assistance in this matter.

Yours sincerely,

Julie Depczynski

Date

Tony Lower

Statement of contribution to publication

Dear Co-authors,

Re: Depczynski J, Dobbins T, Armstrong B, Lower T. **Cancer risk factors and mortality in farm, rural non-farm and urban residents within the 45 and Up Study cohort.** Manuscript prepared for peer review October 2016

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Author contributions

Julie Depczynski conceived and designed the analysis, reviewed the literature, analysed and interpreted the data and drafted and revised the manuscript. Tony Lower interpreted and critically reviewed the data and revised the manuscript. Bruce Armstrong interpreted and critically reviewed the data and provided feedback on the manuscript. Timothy Dobbins critically reviewed the methods and provided feedback on the manuscript. All authors read and approved the final manuscript.

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Yours sincerely,

Julie Depczynski

Date

Tony Lower

Bruce Armstrong

Timothy Dobbins

Statement of contribution to publication

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Chapter 1: Introduction

1.1 The prominence and impacts of cancer

Cancers were responsible for around one third of all deaths in Australia in 2014.¹ One in two men and one in three women will be diagnosed with some form of cancer by the age of 85 years.²⁻³ Most Australians will be affected by cancer either personally or through the experience of a close relative, during their lifetime. However, it has been suggested that improvements in screening, earlier stage cancer detection, diagnostic methods and treatment can have a significant impact on outcomes.⁴

Cancer is a group of diseases characterised by abnormal division and uncontrolled growth of body cells, which can invade nearby tissues and spread to other parts of the body through the circulatory and lymphatic systems.⁴ Cancer can inflict sufferers with months or years of debilitating illness, hospital admissions, surgical procedures, chemotherapy and radiation treatments. For cancer survivors, there is often a cloud of uncertainty that the disease may recur.

The impact of cancer upon individuals and families can be overwhelming in terms of pain, suffering and premature mortality, as well the considerable economic burden. Societal impacts include health system costs, lost productivity and other financial costs. Cancer-related services accounted for approximately \$4.5 billion of the annual health expenditure in Australia for 2008-2009.⁵ More recent figures are only available for admitted patients, but suggest expenditure in the hospital sector of around \$3 billion on cancer related diseases in 2012-2013.² An economic report commissioned by the NSW Cancer Council in 2006 found that the total lifetime financial cost of cancer for those diagnosed in the previous year was equivalent to 1.3% of gross state product.⁶ Most of the economic cost of cancer relates to the burden of disease, of which individuals bore around 90%. Individuals and governments shared around 40% of the direct financial costs of cancer; whilst society, family, friends and employers made up the remainder. In terms of financial cost and total burden of disease, the most expensive cancers to society were lung, colorectal and breast cancers.⁶

1.2 An overview of cancer incidence and mortality in Australia

Registration of cancers, excluding non-melanoma skin cancers (NMSC), is required by law in each Australian state and territory.⁴ Clinical and demographic information about people newly diagnosed with cancer is collected from hospitals, pathologists, oncologists, cancer treatment centres and nursing homes. This information is sent to the National Cancer Statistics Clearing House (NCSCH), and incorporated into the Australian Cancer Database.⁴ Operated by the Australian Institute of Health and Welfare (AIHW), the NCSCH operates under the supervision of the Australasian Association of Cancer Registries. The main source of cancer mortality data is the National Mortality Database which contains information on all deaths where cancer was the underlying cause.

There will be an estimated 130,000 newly diagnosed cancer cases in 2016, the most common being prostate, colorectal and breast cancer, followed by melanoma and lung cancer.² In the same year, there will be an estimated 46,900 deaths, with lung, colorectal and prostate cancer accounting for the most, followed by breast and pancreatic cancer.² The incidence of many cancers rises considerably after 50 years of age, which has implications for the ageing Australian population. While overall incidence of cancers have increased, death rates have declined by around one-fifth in the past thirty years.⁴ This has been attributed to improvements in screening, diagnosis, treatment and survival outcomes for certain cancers. Around 10% of all hospitalisations are related to cancer diagnosis and/or treatment.⁴

Around one third of cancers in Australia have been attributed to commonly known risk factors. The most prominent risk factors are exposure to tobacco smoke and solar radiation, inadequate diet and overweight/obesity and alcohol. Modifying these are likely to significantly reduce the incidence and impact of lung and colorectal cancer, melanoma and breast cancer.⁷ It is not well documented how exposure to these factors might vary between urban, rural non-farm and farm resident populations.

1.3 Urban - rural differences in cancer indicators

Approximately 71% of Australia's 23.8 million people in 2015 lived in 'Major cities', as classified by the Australian Statistical Geography Standard (ASGS).⁸⁻⁹ A further 18% lived in inner regional areas, 9% in outer regional with 2.4% in remote or very remote areas. Differences in the regional cancer incidence and mortality over time have been published in a series of government statistical reports on cancer, rural health and social trends.^{4, 10-11}

1.3.1 Cancer Incidence

Comparative incidence data are available for three overlapping periods for selected cancers by ASGC category spanning 2001 to 2009.^{4, 10-11} These data suggest that compared with major cities, the incidence of all cancers was significantly higher for both inner and outer regional areas; variable or not significantly different in remote areas; but significantly lower in very remote areas. A summary of incidence by major cancer type for regional and remote categories compared to major cities, is provided below.

- *Inner Regional areas:*

Inner regional areas consistently had the highest incidence of all cancers, melanoma, colorectal and prostate cancers, which were all significantly higher than the incidence rates in major cities. Inner regional areas also had significantly higher rates of lung cancer than major cities - although these were lower than outer regional, remote and very remote areas. Cervical cancer and lymphoma incidence rates fluctuated slightly but were generally similar to major cities.

- *Outer Regional areas:*

Outer regional areas were generally second to inner regional areas in terms of incidence rates for most of the selected cancers. Rates were significantly higher than major cities for all cancers, melanoma, colorectal, lung and prostate cancers - but not as high as the rates in inner regional areas.

Outer regional areas had significantly higher rates of cervical and lung cancer than major cities or inner regional areas - but not as high as remote and very remote areas.

- *Remote and very remote areas:*

Incidence rates for all cancers, melanoma, breast and prostate cancers, were generally lower in remote and very remote areas than regional and major cities. Conversely, incidence for cervical and lung cancers were significantly higher than other areas. Patterns varied for colorectal cancer and lymphoma in remote areas from 2008-2012, but were significantly lower in very remote areas than most other areas during the same period.

1.3.2 Cancer mortality

The age-standardised mortality rate for all cancers combined declined over the period from 2002-2012 in each area, but cancer mortality generally increased with remoteness.^{4, 10-11} Major cities had significantly lower death rates than inner regional areas, which in turn had significantly lower rates than outer regional areas. Mortality was highest in remote and very remote areas, being significantly higher than major cities, but not outer regional areas. A summary of comparative mortality for selected cancers by ASGS category is provided below, with reference to major cities.

- *Inner regional areas*

Inner regional areas had the highest rates for breast cancer, colorectal cancer, melanoma and non-Hodgkins lymphoma (NHL) for at least part of the period from 2006-2012. Melanoma mortality rates were the highest and significantly higher than major cities over the whole period. Colorectal cancer mortality was highest in inner regional areas for 2008-2012 of all areas; and significantly higher in inner regional areas than in major cities over the whole period. Breast cancer was highest in inner regional areas from 2006-2010; and NHL mortality highest for 2006-2012, but rates for nHL were not significantly different to those for major cities.

- *Outer regional areas*

Outer regional areas had the highest mortality rates for prostate cancer from 2006-2012; and for colorectal cancer from 2006-2010. These were both significantly higher than rates observed in major cities. People in outer regional areas also had significantly higher mortality due to melanoma and lung cancer than those in major cities.

- *Remote and very remote areas*

Over the whole period from 2002-2012, mortality was generally higher for all cancers, cervical and lung cancer in remote and very remote areas, compared to major cities. Conversely, colorectal cancer, melanoma and NHL mortality rates were generally lower. Patterns of comparative breast and prostate cancer mortality varied.

1.3.3 A regional picture of cancer incidence and mortality

In summary, when cancer incidence and mortality are considered together:

- Major cities tended to have the lowest incidence and mortality rates for both lung and cervical cancer.
- Inner and outer regional areas tended to have the highest incidence and mortality rates for melanoma, prostate and colorectal cancer.
- Remote and very remote areas tended to have the highest incidence and mortality for cervical and lung cancer. They also had the lowest all cancer incidence, but highest all cancer mortality.
- There were variable or inconsistent patterns of incidence and mortality rates by ASGS category for breast cancer and lymphoma.

Generally, incidence and mortality rates for the selected cancers reflected similar patterns i.e. where incidence of a selected cancer was higher, mortality also tended to be higher. For the selected

cancers in both inner and outer regional areas, there was little suggestion of a 'lower incidence/higher mortality' pattern which is sometimes observed in socio-economically disadvantaged populations.¹²⁻¹³ However, it is suggestive of such an effect for 'all cancers' in remote and very remote areas.

Of particular interest over the period, was that the highest incidence and mortality rates for the most common cancers were in regional areas. With the exception of lung and cervical cancers, cancer incidence and mortality did not necessarily increase in a one-direction gradient from lower rates in major cities to higher rates with increasing remoteness.

1.3.4 Cancer survival

Cancer survival is generally considered a measure of the effectiveness of health systems.¹⁴ From 2006-2010, all cancer survival generally decreased with remoteness, but differences were small and not significant. Five-year survival for all cancers was 67% in Major cities, 66% in Inner regional areas, 65% in Outer regional areas and 63% in Remote and Very remote areas.¹⁵ Survival from colorectal prostate and lung cancer from 2006-2010 were highest in major cities, but breast cancer survival was marginally better in inner regional areas and melanoma survival highest in remote and very remote areas.¹⁶ Overall differences in the major cancers were small. Only lung cancer and colorectal cancer survival were significantly higher in major cities; and only breast cancer survival was significantly lower in remote/very remote areas compared to other areas.¹⁶

1.3.5 Other cancer indicators

Other indicators, such as cancer screening and treatment provide an insight into health service access and utilisation in different areas. Separation rates for chemotherapy, for example, have been reported to be significantly higher in regional areas than major cities, but significantly lower in remote areas.¹⁷ This is consistent with cancer incidence trends, which rise in regional areas and fall in remote areas. Women in regional areas were also reported to be significantly more likely to participate in

breast cancer screening compared with those in major cities, while women living in very remote areas were significantly less likely to be screened.¹⁷

Considered together, these indicators suggest there is no simple trend of cancer ‘unwellness’ increasing from major cities toward very remote areas. If anything, a peak seems to occur in inner regional areas, sloping outward from that point by remoteness, with major cities being healthier for most indicators. Factors other than remoteness per se, appear to be important in influencing selected cancer rates.

1.4 Possible reasons for differences between rural and urban people

It has been suggested that rural Australians generally have poorer health outcomes and indicators than their urban counterparts.^{10, 12} Differences in cancer incidence and mortality by rural area may be influenced by a number of factors. People living in remote areas of Australia are reported to have higher rates of risky health behaviours, such as smoking, excessive alcohol use and poor nutrition; and may be disadvantaged in accessing primary health-care services.^{4, 11} Risk factors may vary by geographical area, with socio-economic disadvantage and the higher proportion of Indigenous Australians, being two important underlying influences on health status in rural Australia.^{1, 18}

Socio-economic status, inclusive of educational, employment and income disadvantage, is likely to have a considerable influence on cancer incidence and mortality in rural areas.^{12, 19} Disadvantaged groups consistently have poorer overall health status, with lower life expectancy, higher incidence, prevalence and risk factors for disease and greater rates of avoidable mortality. Additionally, they demonstrate greater use of doctors and hospitals, but are less likely to use preventive health services.¹²

Higher incomes in major cities are consistent with there being a larger proportion of managerial and professional workers in these areas.¹⁹ The proportion of people living on lower incomes generally increases with remoteness. However, after adjustment for housing costs, inner regional areas have

been reported to have a higher proportion of people from low income households, which also reflects their slightly older age profile.^{1, 12, 19} This corresponds with inner regional areas reported to have higher incidence of all cancers, melanoma, prostate, breast, and colorectal cancers; and higher mortality for NHL, melanoma, colorectal and breast cancers.^{4, 12}

Whilst the number of Indigenous Australians is similar between cities and regional areas, the proportion of Indigenous people increases with remoteness.¹⁹ Elevated smoking rates and higher incidence and mortality rates of lung and cervical cancer in very remote areas, coincide with the considerably greater incidence and mortality of these cancers for Indigenous Australians.^{4, 10} Likewise, the lower incidence for all cancers, NHL, colorectal and prostate cancers in very remote areas, are aligned with lower incidence of these cancers by Indigenous status; as are lower mortality from NHL colorectal and prostate cancers in very remote areas.⁴ One exception is breast cancer mortality, which was lower in very remote areas, but higher amongst Indigenous women. This may be related to later cancer stage at diagnosis amongst Aboriginal women in very remote areas; and /or difficulty in providing the required cancer services, for breast cancers¹³. Further, this may be compounded by considerable family and economic barriers to travelling and staying far from home for extended periods. In 2006, 40% of Indigenous Australians were in the bottom 20% of mean equivalent household incomes.¹⁰

Geographic distance (the tyranny of distance), may play a role as rural Australians have been reported to have significantly lower levels of utilisation and/or access to health care services.¹² However, it is not known if issues of access to services for initial consultation and diagnosis result in presentation when cancers are at a later stage of development and are less amenable to treatment interventions.¹² Further, it is possible that distance could impact on decisions regarding the types of medical treatment received; including referral to specialist cancer centres versus regional general hospitals.²⁰

1.5 A demography of Australian farmers and farm families

1.5.1 Australian farmers

Agriculture is a major employer in rural Australia, with around a quarter of men in outer regional and remote areas employed in the sector.¹² Australian farmers can be considered a rural sub-population, with unique characteristics insofar as their employment, lifestyle, potential environmental exposures and socio-economic factors. By occupation, farmers and farm managers:

“... plan, organise, control, coordinate and perform farming operations in agricultural establishments. Tasks performed typically include planning and coordinating the operation of hatcheries and crop production; breeding and raising livestock; monitoring and maintaining the health of stock; identifying and controlling environmental toxins, weeds, pests and diseases; organising and conducting farming operations such as maintaining buildings, water supply and equipment; managing business capital, monitoring market activity and planning production to meet contract requirements and market demand.”²¹⁻²²

For ABS statistical purposes farmers are those who reported that their main occupation was a farmer or farm manager on census night. In 2011, there were 157,000 farmers in Australia, most being mixed crop and livestock farmers (22%), beef cattle farmers (20%), dairy farmers (8%) and sheep farmers (7%).²³ Around one third of Australia’s estimated 120,000 farms are located in NSW.²⁴ Farmers are generally older than other workers (median 53 yrs in 2011); more likely to continue working well beyond retirement age (23% aged 65 years or over); more likely to be self-employed; work longer hours (50% over 49 hours a week); and have lower disposable income with higher household wealth.^{19, 21, 23}

1.5.2 Farming families

It has been estimated that 99% of farms in Australia are family businesses, passed on to successive generations.²⁵ In 2011, there were 93,300 farming families in Australia where the family reference

person and /or their spouse or partner, reported that their main occupation was a farmer or farm manager.²¹ Generally, farm families are:^{19, 21}

- more likely to be a couple living by themselves (48%) than other families (38%).
- slightly larger than other families, average 4.0 members compared to 3.7 for other families.
- less likely to be one parent families, 3% vs. 16% for other families.
- likely to be supported by women:
 - one third of farmers are women.
 - one third of women in farm families also have off-farm work, whilst simultaneously supporting operation of the farm.
- more locally connected, with volunteering rates twice as high as other families - partly related to service provider gaps in smaller communities and an older age-skew.

The number of farming families has been steadily declining over recent decades.²¹ Contrary to popular belief, the greatest declines coincide with periods of better commodity prices, where improved financial capacity enables farmers to expand and buy-out neighbouring farms; whilst hard times see farmers delaying retirement or waiting until conditions improve.^{19, 21} However, poorer economic conditions for farm families are likely to affect the capacity to employ other farm workers, with a decline in farm worker numbers under poorer economic conditions.²¹

In the absence of more recent data on the distribution of farm families, 2001 Census data suggests that around 6% of farm families are located near/around major cities, 34% reside in inner regional, 46% outer regional and 14% in remote and very remote areas.¹⁹ Most farming families live in inner and outer regional areas, but this varies with farm type. Intensive small farms (e.g. market gardens) and dairy farms, tend to be located closer to Major Cities and in Inner Regional areas; whilst over 50% of all sheep farmers and mixed crop/livestock families live in Outer Regional areas.¹⁹ Whilst more farming families lived in Major Cities than in Very Remote areas, farm families comprised 10% of all families in Very

Remote areas, compared to only 0.2% of families in Major Cities.²¹ As such, the health of this very small group is unlikely to affect the health indicators of Major Cities.

There is a lack of definitive data on the proportion of occupational farmers, farm managers and farm workers and their families who actually live on farm. Using 'urban centre' as a measure, an estimated 13% of farming families lived off-farm in urban centres over 1,000 people in 2001, with the primary farmer travelling to work on farm.¹⁹ Another proxy indicator provided by census data is stated method of travel to work. In 2011, 58% of 42,595 farmers and farm managers in NSW, either walked to work or worked from home.²⁶ This is likely to be a considerable under-estimation, as larger landholdings may require vehicular transport to farm work areas (which may be a preferred option for older farmers) and farmers may also own multiple landholdings requiring transport. Allowing for such shortcomings, a conservative mid-range estimate between the two sources might suggest that at least three quarters of commercial farmers live on farm.

It is not known how many non-commercial or lifestyle farms there are in NSW, but a third of all commercial farms are less than 50 hectares in size.²¹ Farm exposures and activities may be similar, depending on whether work or leisure purposes dominate. Conversely, some farm family members and lifestyle farmers may have little to do with farming activity per se; and their lifestyle and access to services may be similar to other rural people. These are inherent limitations associated with defining farm and non-farm residents into neat categories of exposure or health risk. We do know however, that people who either live or work on farms have a unique set of characteristics associated with life and work on farm; and they constitute a sizeable rural population for which there is very limited information about cancer indicators and risk factors.

1.6 Previous studies of cancer in Australian farmers

Whilst rural cancer incidence and mortality are reported in regular statistical reports on cancer in Australia,^{4, 10-11} only two studies have been published that specifically address these issues in farmers as an occupational or residentially defined group. A case-control study was conducted of lymphohaematopoietic cancers in Tasmania from 1972–80. Farmers, miners, foundry workers and hairdressers had elevated risk compared to other occupations, with risk to farmers varying with age at diagnosis, sex and region.²⁷ Families of older farmers were also at higher risk. A related study of this cohort reported that farm residence in early life also yielded higher relative risks for chronic lymphocytic leukemia and acute myeloid leukemia, particularly in orcharding and dairying.²⁸

Another study compared ABS mortality data for male farmers aged 25-74 years, with other Australians between 1999-2002.²⁹ Farmers had significantly higher mortality for all cancers and cancer of the prostate and lymphohaematopoietic systems than other Australian men. No other studies have reported on incidence and mortality by occupational grouping since the ABS ceased to report by this category in 2002.

1.7 Cancer risk factors in farmers

Previous studies have suggested higher rates of cancer mortality in rural areas may be attributed to higher risk alcohol consumption and smoking rates; plus educational, employment and income disadvantage.^{10-12, 21} However, there is limited information as to whether lifestyle or socio-economic risk factors for cancer differ between farmers and other rural people in Australia. No significant differences were noted in lifestyle factors between farm and non-farm participants at an agricultural field day health promotion program in rural NSW.³⁰ Likewise, alcohol consumption patterns, waist circumference, overweight and obesity, physical activity and smoking behaviours between farm and non-farm groups were not dissimilar in the 2008 NSW Population Health Survey.³¹⁻³² Several of these factors will be explored further in the primary research study.

There are also a range of potential environmental cancer risks including pesticide and chemical exposures, commodity specific exposures and sun exposure that may occur in an agricultural setting. A recent review assessed 103 studies on farm pesticide exposures and cancer risks published from 1991-2010 for selected cancer sites.³³ When cross-checked with the Australian Pesticide and Veterinary Medicines Association (APVMA) online chemical register in November 2016, 7 of the 21 chemical formulations listed in the review as being associated with increased cancer risk were registered for use in Australia.³³⁻³⁴ The review concluded that some chemicals in every pesticide class were found to have significant associations with several cancer sites, particularly amongst chlorinated, organophosphate and carbamate insecticides and phenoxy and triazine herbicides. However, the review also pointed out that there are over 800 active ingredients and thousands of pesticide formulations on the market. Importantly, the review concluded that one of the 'major challenges' of epidemiology is the identification of whether specific compounds are responsible for specific cancer risks; and research should focus on specific exposures to individual pesticides and specific cancers, controlling for potential confounders. A lack of precision in exposure measures and inadequate replication of studies also contributed to the systemic methodological problems in detecting pesticide associations from epidemiological studies.³²

Seventeen studies have been published since 2002 on associations between cancer risk and commodity type. There has been a lack of clear evidence on associations of different commodity groups with breast, colorectal or prostate cancers, or melanoma.³⁵⁻³⁸ Lymphohaematopoietic subtypes have been the most studied. Positive associations were more commonly reported for cropping and horticulture than for livestock in regards to lymphoma and leukaemia, although myeloma has been associated with sheep production.^{35-36, 39-41} Negative associations were more commonly reported for livestock groups than for cropping/horticulture groups. In particular, dairy exposure and lung cancer were found to be negatively associated in three out of four analyses; with the protective effects of endotoxin exposure one reason suggested for these findings.^{36, 42-43}

Sun exposure is another risk factor likely to be greater for those living and working on farms. One recent Australian study assessed this in the context of occupational carcinogens across industry sectors. In agriculture, the most common environmental carcinogen was solar ultraviolet radiation associated with working outdoors. Exposure to diesel engine exhaust, benzene, polycyclic aromatic hydrocarbons were likely to be associated with using diesel powered equipment, refueling petrol powered equipment and repairing motors and farming equipment.⁴⁴

1.8 Health services access and utilisation

Access to / utilisation of health services such as suitable screening, diagnosis and treatment facilities may be limited in rural areas, but it is not known if this is any different for farming families than for other rural people. In the absence of sufficient studies, questions remain as to if and why some cancers may be elevated in Australian farmers.

1.9 Research objectives

It is currently not known if elevated mortality rates for cancer previously reported in Australian farmers is related to higher incidence of these cancers, later presentation, later diagnosis or access to best treatment.²⁷⁻²⁹ Additionally, the relative contribution and/or association of behavioural, environmental, health service utilisation and other rural factors with cancer mortality and incidence in farmers is limited.

Focusing on farm residents, this study aimed to identify if there are variations between NSW farm, rural non-farm and urban residents in the 45 and Up Study in relation to:

1. Incidence and mortality from selected major cancers
2. Screening rates, stage at diagnosis and selected cancer therapies
3. Common risk factors associated with these cancers

In addition to the above, there was interest in whether the two rural groups might differ from the urban group - particularly in relation to baseline risk factors and health service related indicators. The series of studies undertaken will add to the body of evidence on cancer risk in these population groups. Identifying potential disadvantage and strengthening the evidence base on which health policy and resourcing decisions are made, is an important role of epidemiological and health services research.

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Chapter 2: Literature review

2.1 Objectives

The objectives of this literature review were to examine differences between farmers and non-farmers in the incidence, mortality, screening, stage at diagnosis, treatment and survival outcomes for 'all cancers' and selected major cancers. A review of environmental risk factors associated with living or working on a farm and possible associations with cancer was initially considered. However, analysis of environmental risk factors could not be undertaken in the primary research project of this thesis, as exposure information was not available. Therefore, it was decided not to include this component as part of the literature review for this body of work.

2.2 Methods of selection, identification and assessment of studies

A review protocol was established prior to conducting the review to assist in the systematic identification and assessment of relevant studies. Eligibility criteria were also developed to guide selection of appropriate studies. The protocol and eligibility criteria are provided in the Appendix to Chapter 2.

A broad initial search of the literature on cancer in farmers was undertaken to maximise capture. This yield was further compartmentalised into a set of smaller reviews, focusing on particular elements or cancers. The most detailed of these related to prostate cancer risk, the subject of a paper submitted for publication.

English language abstracts of both primary studies and reviews were searched within Medline, Web of Science, BioMed Central, Cochrane library, Scopus, Embase, Informit, Proquest and Google Scholar. Search terms used were based on the following strings:

- Farm* or Agricultur* or occupation*; AND
- (cancer OR melanoma OR lymphoma); AND

- (incidence OR presentation OR diagnosis OR treatment OR screening OR mortality OR death OR survival OR risk).

These search concepts were adapted for each database as required - and were confined to appearance in the title or abstract, so that cancer and 'farming' / 'occupation' were the focus of the research. The broader scope search had no year limits, but these were restricted for some of the sub-reviews. The search was initially inclusive of all major cancer groupings with cancer status based on diagnoses using ICD9 or ICD10 classifications, as usually reported by population-based cancer registries.¹ Details on region and 'farmer' status were required. A summary of steps used to retrieve and categorise the literature are shown in Figure 2.1.

Standard quality tools were used to guide selection, categorisation and assessment of individual articles. These were the (1) Strengthening of reporting of observational studies in epidemiology (STROBE) statement;² the (2) Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies (EPHPP);³ (3) tools developed by the Critical Skills Appraisal Program (CASP);⁴ and the 'Grading of Recommendations, Assessment, Development and Evaluation (GRADE)' approach for assessing the quality of the body of evidence across studies.⁵ Criteria were also developed to standardise statements made by different component studies, on whether a significant excess or deficit of a selected cancer risk in farmers existed. Determination considered both the narrative conclusion of the study (or review study), as well as quantified results within the component study. These criteria appear in the Appendix to Chapter 2.

For reviews and primary studies of incidence and mortality, the ratio or percentage of reviews reporting a clear excess or deficit of cancer risk in farmers, out of all reports, was determined and formed the basis of summary of findings.

2.2.1 Methods relating to review studies

Reviews selected were confined to those addressing results of epidemiological, population-based studies - either of cohort, cross-sectional or case-control design. Narrative overviews, comments and issues papers were not included, nor reviews of health promotion evaluations; ecological studies, attitudinal and behavioural studies. Reviews with selective reporting of results were not included (e.g. reports of positive/significant results only); nor previous versions of reviews where updates were available.

The methodology of reviews and their component studies was assessed to ensure review conclusions were based on component studies of sufficient quality.²⁻⁵ Appropriate non-farmer comparison groups needed to be defined. Other criteria were the reporting of findings for three or more diseases and/or results for several occupations; age-gender standardisation with risk estimates for several cancer sites; and studies with sufficient data for determining confidence intervals. Risk estimates could be expressed as:

- standardised mortality rates or ratios (SMR)
- standardised incidence rates or ratios (SIR)
- relative risk (RR)
- hazard ratio (HR)
- odds ratio (OR)

2.2.2 Methods relating to primary studies

This component of the review retrieved observational, epidemiological, population-based studies of cohort, cross-sectional or case-control designs. Regions, gender and age groups needed to be defined. Studies compared urban populations/participants and/or rural 'non-farm' groups with 'farm' groups. Farmer groups (men or women) were defined by:

- occupational grouping - 'farmer' or 'farm / agricultural worker'
- farm labour/union membership
- 'farm' residential status

Non-farmer groups (men or women) were defined either by:

- 'non-farmer' occupational grouping
- 'non-farm' residence (rural or metropolitan)
- 'whole' population or 'all' occupations in a jurisdiction

Some further restrictions on the criteria for inclusion were placed on primary research articles. Firstly, only those arising from populations classified as 'very highly developed' according to the United Nations Index for Human Development were included.⁶ The rationale for this is to enable valid comparisons between findings for this review and earlier reviews, which also focused on farmers located in advanced economies.

For primary studies, the scope was restricted to the more commonly occurring cancers, or those that previous reviews suggested might be more prevalent in farming populations. These were breast, colorectal, lung, lymphohaematopoietic cancers (lymphomas, myeloma, leukaemias), melanoma and prostate cancer. In addition, only articles published from 2003 onward were included. This decision was based on: (1) previous publication of a number of large reviews which had encompassed most of the literature before 2002; and (2) an interest in assessing whether some change in the risk profile of major cancers in farmers over the past 10 years had occurred, since previous reviews had been published. However, there were a lack of reviews and primary research articles on health service-related factors, such that restrictions on year of publication or cancer type for this category of studies was not applied.

2.2.3 Retrieval and selection overview flowchart

A flowchart summarising the retrieval, selection and categorisation of studies is shown in Figure 2.1.

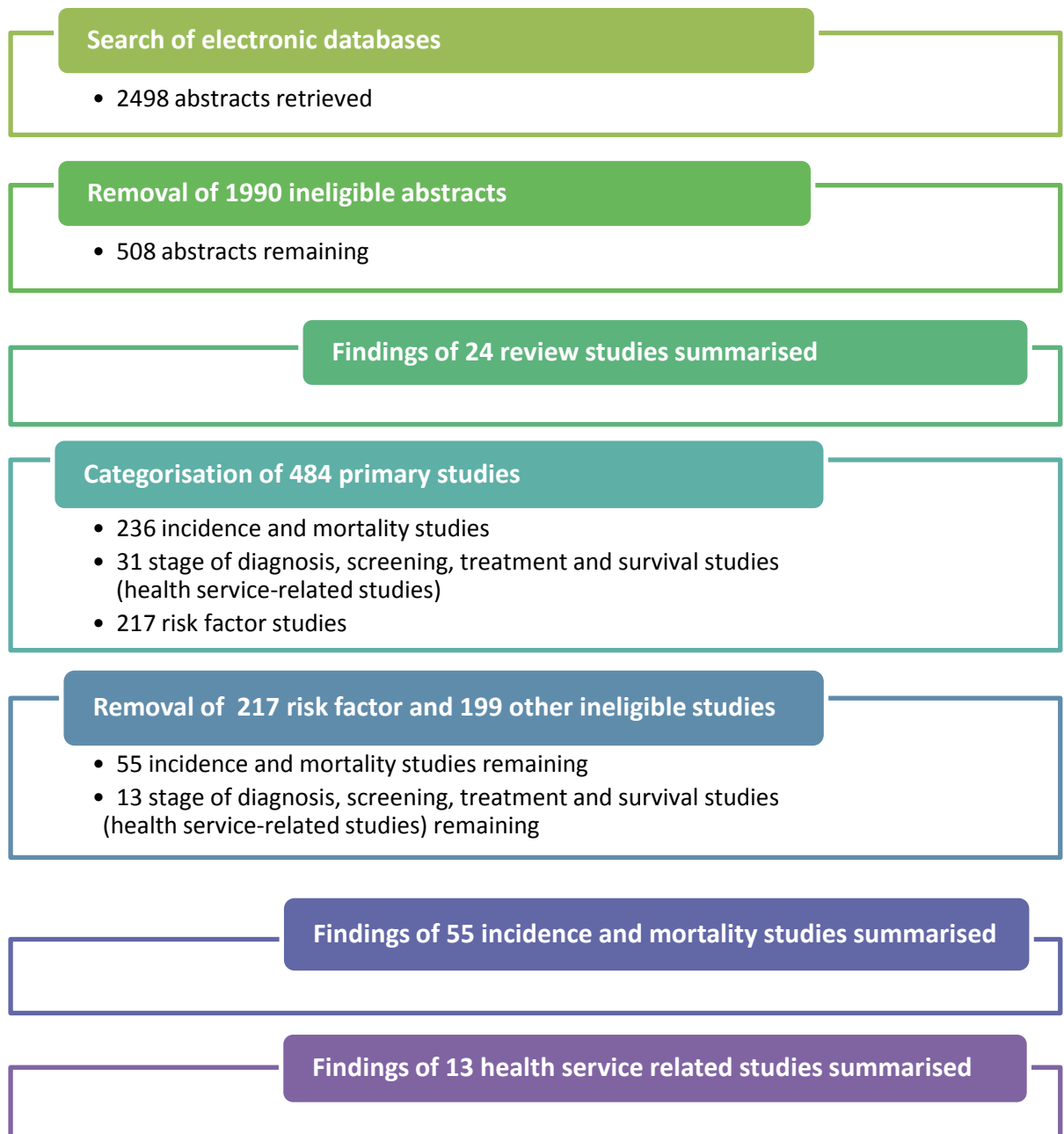


Figure 2.1: Retrieval and assessment flowchart for studies published 2003-2016 related to cancer incidence, mortality and health service factors in farm compared to non-farm groups

2.3 Summary of findings from previous reviews

The first summary is an overview of previous reviews of cancer incidence and mortality in farmers compared to non-farmers. Further summaries are based on primary studies relating to: (1) comparative cancer mortality/incidence; (2) a review focusing on prostate cancer incidence and mortality in farmers published in a peer-reviewed journal; and (3) a summary of health service related studies comparing farm and non-farm groups.

2.3.1 Cancer risk

Twenty four reviews were identified addressing comparative cancer incidence and mortality in farmers, published between 1985 and 2016.⁷⁻²⁹ Cancers where 50% or more of reviews reported a significant excess in farmers out of all reviews of such cancers, were lip cancer (5 of 6 reviews); multiple myeloma (6 of 7); Hodgkin's lymphoma (5 of 6); leukaemia (3 of 6); prostate cancer (7 of 11); and brain cancer (4 of 8). Over 40% of reviews on melanoma, NHL and cancers of the stomach and nasopharynx, also reported a significant excess risk in farm groups.

Cancers where 50% or more of reviews reported a significant deficit in farmers were for all cancers combined (6 of 7 reviews); bladder cancer (5 of 7); lung cancer (6 of 9 reviews); esophageal cancer (3 of 5) and colon cancer excluding rectum (4 of 6). Cancers showing no real difference between farmers and non-farmers were cancers of the female reproductive system, breast, non-melanoma skin cancers, rectum, testes, connective tissue and liver.

Figure 2.2. indicates the general direction of cancer risk in farmers for some of the more common cancers, suggested by the percentage of reviews reporting significant excess and/or deficit out of all reports. Note that it is possible for each cancer to have two bars on the x axis, or no bar at all. For example, one out of nine lung cancer reviews (11%) reported a significant excess as represented by the

blue bar; whilst six of nine reviews (67%), reported a significant deficit of risk, represented by the red bar. No bars are shown for breast cancer, reflecting the neutral findings of reviews of this cancer.

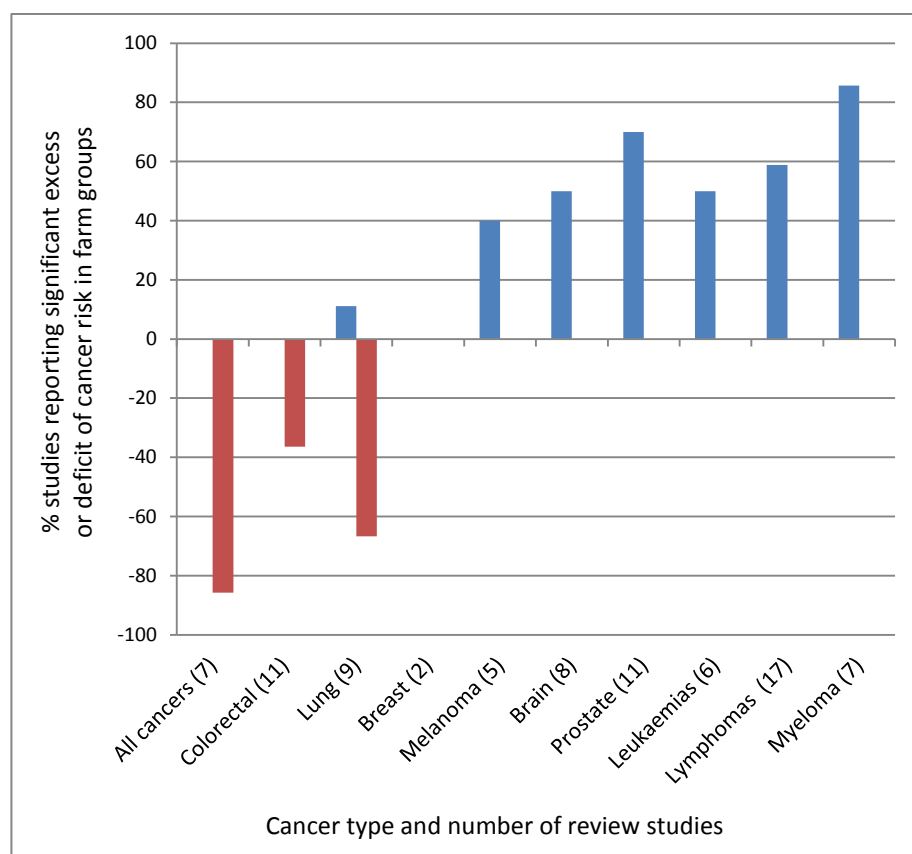


Figure 2.2: Summary of review study findings for risk excess or deficit of selected cancers in farmers compared to non-farmers from reviews published 1992-2014

2.3.2 Limitations and conclusions

Others have described inherent problems in reviewing and comparing component studies that use disparate methodologies.^{7, 30} These issues include:

- imprecise measures of 'farm exposure' (e.g. residency, occupation, registers, self-report, broad groupings, approximating exposure times/degree or intensity of exposure)
- small number of studies, small sample sizes

- heterogeneity - variability in focus, scope, methods, measures, farming systems, regions, time-spans
- difficulties identifying and controlling for unknown confounders (e.g. multiple exposures, socioeconomic variables, genetics)

The evidence on cancer risk in farmers from previous reviews is suggestive of a deficit for all cancer, bladder, colorectal, lung and oesophageal cancers. Meanwhile the data suggest an excess risk for lip, prostate, some lymphohaematopoietic cancers and possibly brain cancers. However, the strength of evidence for excess or deficit of different cancers in farmers is relatively weak. This is largely due to the low volume of studies for each cancer type; and inconsistent methodological approaches which make comparisons difficult.

2.4 Summary of findings from primary studies of cancer incidence and mortality

Fifty five incidence and/or mortality studies published from 2003-2016 met the eligibility criteria addressing selected cancers. There were 41 incidence studies, 13 mortality studies and one study that reported on both incidence and mortality. Overall directions of findings for each selected cancer type are summarised in figures 2.3 and 2.4. These represent the percentage of articles reporting a significant excess or deficit of cancer risk in farm groups, out of all studies for each cancer.

2.4.1 Cancer incidence

The lymphohaematopoietic cancer grouping had the highest percentage of studies finding excess incidence in farm groups. Seven of 15 studies of leukaemia (46%) and six of 14 myeloma studies (43%) reported significant excesses in farmers, with remaining studies finding no significant differences. Lymphoma, including NHL was the most studied of the selected cancer groups, with six of 23 studies (26%) reporting an excess in farmers, but over two-thirds finding no difference between groups.

For prostate cancer, three of 12 studies (25%) also reported significant excess incidence, with one reporting a deficit in farm groups. On balance, studies suggested an overall deficit of all cancer, breast, colorectal, lung and melanoma cancers, in farm groups. Significant deficits were reported in six of seven studies of all cancer (86%) and seven of nine colorectal cancer studies (78%). Over half of all breast cancer studies (7 of 13) reported deficits in farm women, although two reported an excess. Findings for melanoma were mixed with three of nine studies (33%) reporting a deficit, one reporting an excess and five reporting no difference in melanoma incidence between farm and non-farm groups. Lung cancer incidence was significantly lower in farm groups in nine of 11 studies (82%), the most prominent of the selected cancers regarding reduced incidence in farmer groups.

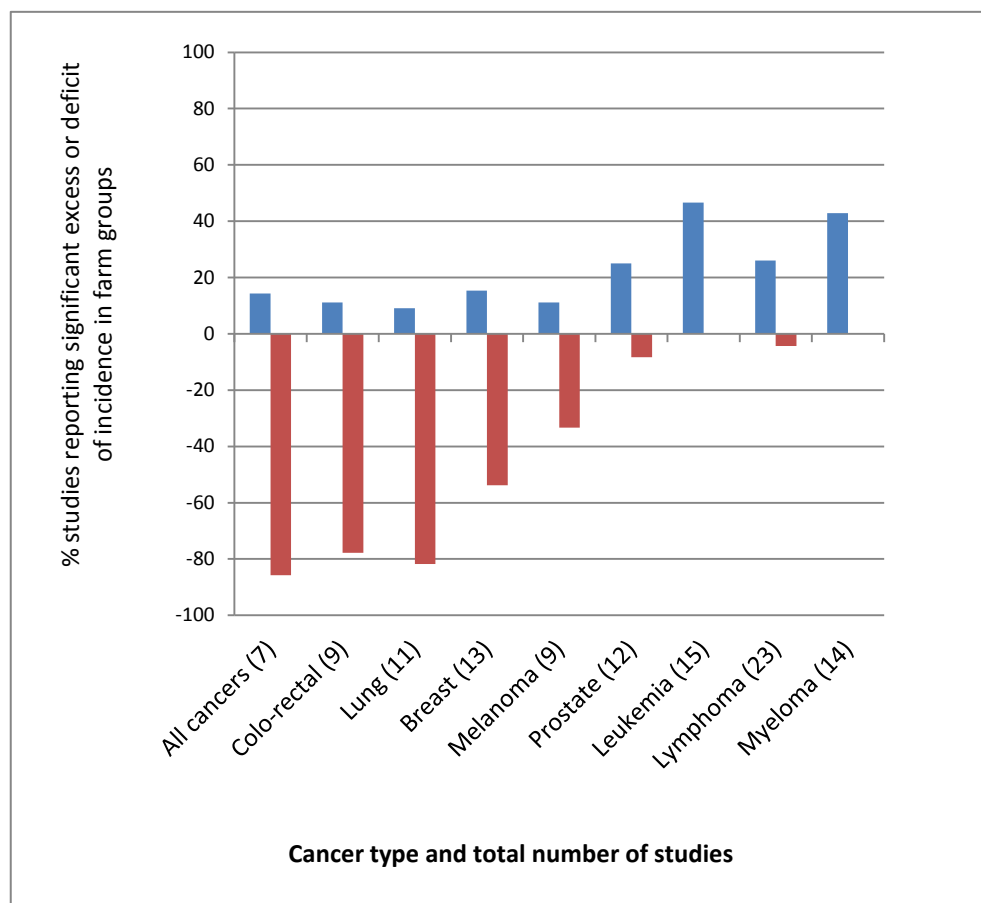


Figure 2.3: Direction of findings for incidence of selected cancers in farm compared to non-farm groups, from 42 studies published 2003-2016

2.4.2 Cancer mortality

There were 14 studies comparing cancer mortality between farm and non-farm groups from 2003 to 2016. Ten of these reported on all cancer mortality, of which three studies found an excess (30%); two found no difference (20%); and five studies (50%) reported a deficit in all cancer mortality in farm compared to non-farm groups.

The only selected cancers with findings for excess mortality in farm groups were prostate and lymphohaematopoietic cancers. Three of 12 studies (25%) found a significant excess of lymphohaematopoietic cancer in farm groups; although eight (67%) reported no significant difference. Similarly, three of ten prostate cancer studies (30%) reported a significant excess in farm groups, although two studies reported deficits (20%); and five studies (50%) found no significant differences between farm and non-farm groups.

For melanoma, none of the seven studies reported either an excess or deficit of mortality in farm groups. The remaining cancers reported deficits or neutral findings. Six of 10 lung cancer studies (60%); four of seven colorectal cancer studies (57%) and two of six breast cancer studies (33%), found deficits in mortality in farm compared to non-farm groups.

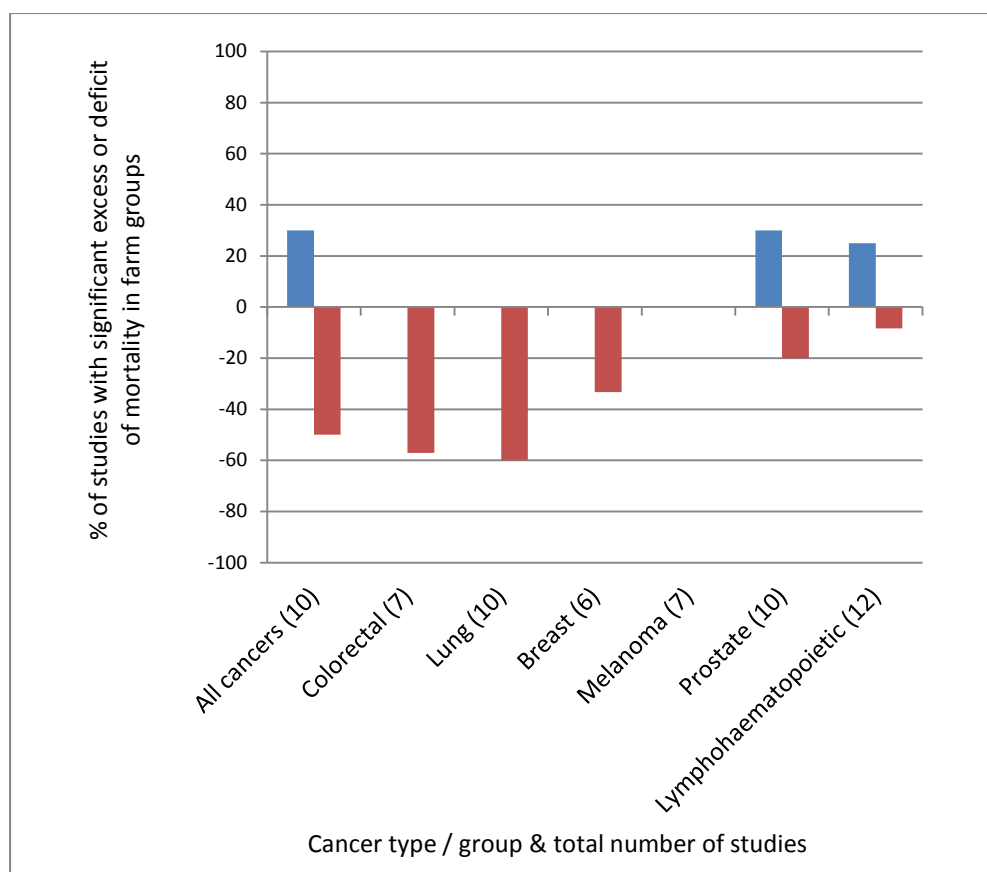


Figure 2.4: Direction of findings for mortality from selected cancers in farm compared to non-farm groups, from 14 studies published 2003-2016

2.4.3 Limitations and conclusions

As for 'previous reviews', there were limitations in the strength of conclusions which could be drawn from our review of primary studies of cancer incidence and mortality. This was largely due to the heterogeneity of component studies; different methodologies used; the small numbers of studies reporting findings on particular cancers; and the difficulty component studies reliant on secondary data sources had in controlling for confounders.

There were some consistencies with the findings of previous reviews - and some differences. The majority of studies have reported neutral findings, such that the strength of evidence for an excess risk in farm groups is perhaps weaker than in previous reviews. The overall direction of findings tends

toward neutral or negative risk in farm groups. In particular, this review suggests that for farm groups, there may be a:

- deficit in all cancer and lung cancer risk, similar to conclusions of most previous reviews.
- deficit in colorectal cancer, compared to mainly neutral/some deficit of risk suggested in previous reviews.
- deficit or neutral risk of breast cancer, compared to neutral findings of previous reviews.
- neutral risk of melanoma, compared to neutral/excess risk suggested in previous reviews.
- neutral or mixed findings for prostate cancer, compared to neutral/excess risk suggested in previous reviews.
- neutral to excess risk of some lymphohaematopoietic cancers, compared to an excess risk suggested in the majority of previous reviews.

It is possible that the cancer incidence and mortality risk of farmers or farm groups has improved over the past decade. However, it is also possible that study measures have changed and greater control for confounders has been achieved in more recent studies. These issues are discussed more fully in the review of studies that focus on prostate cancer risk (Appendix to Chapter 2).

Considering the broad scope of this review, only two components are presented in greater detail. These relate to: (1) prostate cancer incidence and mortality risk; and (2) comparison of health service related factors between farm and non-farm groups.

2.4.4 Prostate cancer incidence and mortality risk

Prostate cancer risk was explored more fully as it is the most frequently diagnosed cancer in men in the developed world;³¹ and studies on cancer risk in farmers have historically been considered useful for providing insights into safe work practices and the development of cancers in the general population.^{9, 32} Some have proposed that elevated cancer risk in farmers may be related to lifestyle factors or pesticide

exposures, but this remains unclear.^{15, 27} We had a particular interest and a capacity in our primary study to contribute to the evidence on the role of lifestyle risk factors in cancer risk in farmers. Meanwhile, prostate cancer incidence and mortality risk per se, was the subject of a paper published in 2014 and is included in the Appendix to Chapter 2.

Publication 1: Depczynski, J and Lower T. 'A review of prostate cancer incidence and mortality studies of farmers and non-farmers, 2002–2013' *Cancer Epidemiology*. December 2014. Volume 38, Issue 6, Pages 654–662.

2.5 Summary of findings involving health service related factors

Given the geographic dispersion of rural Australia, there is potential for health service related factors to have a considerable impact on cancer identification and treatment. A summary of findings are described below for (1) stage at diagnosis or treatment; (2) cancer survival outcomes; and (3) cancer screening. Additional information on each component study and the quality assessment process, are provided in the Appendix to Chapter 2.

2.5.1 Stage at diagnosis and treatment

Only five studies addressed the issue of differentials in stage of cancer diagnosis between farmers and non-farmers. Three studies found that farmers and/or agricultural worker groups were significantly more likely to be diagnosed at 'later stage' compared to non-farmers for all cancers combined, prostate cancer and testicular cancer.³³⁻³⁵ In contrast, there were mixed findings in studies that assessed colorectal cancer. For men, two related Californian studies found later stage colorectal cancer diagnosis in agricultural workers;^{33, 35} but a French study found no such differences between farmers and other social-professional groups.³⁶ There were no significant differences in stage at diagnosis of colorectal cancer in women in any of these studies.

There were no significant differences in stage at diagnosis for laryngeal cancer between farmers/agricultural workers and non-farmers, although different patterns of presentation were noted.^{33, 37} The two Californian studies found no significant differences between agricultural workers and non-farmers for melanoma, myeloma, NHL or cancers of the breast, cervix, lung, brain, liver, pancreas, soft tissue, stomach, thyroid, reproductive or urinary systems.^{33, 35}

Only one study reported on treatment differences between farmers and non-farmers. There were no significant differences for treatment of colorectal cancer by surgical resection between farm and non-farm men; but farm women were significantly less likely than other social-professional groups to undergo surgical resection for colorectal cancer.³⁶

2.5.2 Survival outcomes

Five studies addressed the issue of differences in 'survival outcomes' between farmers and non-farmers. One Californian study reported on crude survival rates in Californian agricultural workers and non-farmers for all cancer and 20 cancer sites.³³ After adjusting for age and stage at diagnosis, male agricultural workers had better survival outcomes for NHL. A Swedish study in the 1980's reported crude survival deficits in farmers for all cancer and for cancers of the bladder, colon, kidney, prostate, rectum and testes. However, this study did not control for confounders and did not report on the significance of differences presented.³⁸ Therefore, caution is required with interpretation of these results and they shall not be considered in the balance of evidence. No significant differences were found in survival outcomes between farmers and non-farmers for laryngeal cancer.^{33, 37} There were mixed findings for colorectal cancer survival outcomes. After adjusting for confounders, two European studies reported poorer colorectal cancer survival outcomes for farmers;^{36, 39} with a Californian study finding no difference.³³

2.5.3 Cancer screening

Six studies from the United States addressed the issue of differences in 'cancer screening' between farmers and non-farmers. Two used 'routine' or 'primary care' check-up as an indicator for screening of 'any' cancer.⁴⁰⁻⁴¹ No difference in routine primary care check-ups were found for women; although one did report that farm men had less frequent check-ups than non-farm men.⁴¹ There was no difference for either gender in the frequency of 'multiple' screenings tests as recommended in respective guidelines (colorectal, prostate, skin cancer).⁴¹ Generally, there was insufficient evidence of a difference in screening for all cancers between farmers and non-farmers, at primary care or general health check-ups.

Breast cancer screening practices were assessed in five studies. One found that farm women in Wisconsin reported health insurance to be a problem in accessing preventative screening, but this did not affect mammogram screening rates per se.⁴² Another study likewise found no difference in either mammogram usage or clinical breast examinations amongst farm and non-farm women in Iowa.⁴⁰ After controlling for related variables, residence was not associated with screening practices in Colorado, except farm women were less likely to have a recent breast examination than metropolitan women.⁴³ Another study in Iowa reported mixed results, with farm women 40-49 yrs more likely to have a mammogram in the past two years, but a higher proportion of non-farm women over 50 years had a mammogram in the past year.⁴¹ Higher mammogram usage in farm women compared to state data was reported in Michigan, but the comparability and significance of this difference was not made clear.⁴⁴ On balance, most results were neutral, with little evidence of a difference in breast cancer screening rates between farm and non-farm women.

Cervical cancer screening practices were also analysed in five studies. Farm residents in Wisconsin were significantly less likely to have Pap smears at recommended time intervals;⁴² and farm women in Kentucky and Louisiana had lower crude rates of cervical cancer screening compared to 'adjusted' state-

wide data.⁴⁵ Both these studies however, were of only fair quality with methodological shortcomings relating to reporting of results and/or comparison of crude rates for farmers with adjusted state data (see Appendix 2). There were no differences in screening in the latter study for women in Texas;⁴⁵ nor for women in a Colorado study.⁴³ Likewise, there were no differences in screening reported in the more methodologically robust studies of women in Iowa.⁴⁰⁻⁴¹ Given that the better quality studies had neutral findings, there is little evidence overall to support a difference in cervical screening rates between farm and non-farm women.

Prostate and skin cancer screening rates were compared in only one study, from Iowa.⁴¹ Farmers over 50 years were significantly less likely to have had a prostate examination, although there was no significant difference when the larger 40+ years age group was assessed. However, both farm men and women over 40 years, were significantly more likely to have skin cancer screening than non-farmers, although the difference for men over 50 years became insignificant. Whilst suggestive of a difference in farmer/non-farmer screening rates amongst older men, more studies need to be conducted to confirm these findings for skin and prostate cancer.

Colorectal cancer screening rates were analysed in two studies, with mixed findings. Farmers in one study were less likely to have had stool blood screening for colorectal cancer in the past year, but there was no difference compared to non-farmers after two years.⁴⁰ Another study also found no difference between farmers and non-farmers in colorectal screening in those over 50 years of age, although older farm women were more likely to have had a sigmoidoscopy in the past five years than non-farm women.⁴¹ In the context of Australian recommendations for faecal occult blood testing (FOBT) for those 50 years and over every two years,⁴⁶ there is little evidence of a difference between farmers and non-farmers, if using Australian guidelines as indicators.

All six screening studies ran regression models to assess predictors for cancer screening. Farmer status was not a predictor of 'multiple screening' or mammogram usage;⁴¹⁻⁴³ although one found it as a

predictor of non-compliance for breast examinations.⁴³ There were mixed results in three studies as to whether farmer status was a predictor of cervical screening.^{42-43, 45} Other factors showing positive or mixed predictive value for non-compliance with screening were no preventative health insurance, age, income, educational level and having no primary health care provider.⁴¹⁻⁴⁵ Factors showing no predictive value for screening compliance were 'time to health care facility', perceptions of general health, or a perception that health insurance was a problem to obtaining care.^{42-43, 45}

2.5.4 Limitations and conclusions

Overall, there were very few studies that assessed differences in stage at diagnosis or treatment of cancers between farmer and non-farmers groups in this review. Whilst individual studies were generally of good quality, the quality of the body of evidence across studies based on the 'GRADE' Approach was low.⁵ This was largely due to limitations of observational study design typical of epidemiological research. Overall, the level of evidence on differences in stage at diagnosis between farmer and non-farmers is low or insufficient, from both quantity and quality perspectives.

For survival outcomes, individual studies were generally of good quality, with the exception of one.³⁸ However, the quality of the body of evidence across studies remains low, due to the heterogeneity of studies and the insufficient number of studies addressing this question. Results suggest there may be a differential in colorectal cancer survival outcomes, but generally there was insufficient evidence of a difference in cancer survival outcomes between farmers and non-farmers for most selected cancers.

Linked to the problem of heterogeneity and low volume of studies, comparing countries with different health systems and health insurance schemes may have contributed to the lack of a clear direction of findings. Policies and structures of health systems influence the quality and access of health services for different groups, which in turn affected stage, treatment and survival; and perhaps the likelihood of screening in different countries.

The quality of individual studies on comparative screening ranged from good;⁴⁰⁻⁴¹ through to fair;^{42-43, 45} to one study of borderline quality regarding its screening practices component.⁴⁴ All studies were of cross-sectional or baseline survey design, with quality of the body of evidence across studies again low using the GRADE criteria.⁵ There were few studies addressing comparative screening practices of farmers and non-farmers. For colorectal, prostate and skin cancers, there were an insufficient number of studies to draw conclusions about comparative screening practices. There were more studies on breast and cervical screening, with little or no evidence for a difference in screening practices between farmers and non-farmers.^{40-42, 45} The overall evidence for a difference in screening practices between farmers and non-farmers is lacking; and where present, suggested little to no difference between farm and non-farm groups.

This component review of health service related factors has established there is a general lack of knowledge on comparative stage of cancer diagnosis, treatment, survival and screening practices between farm and non-farm population groups. One of the objectives of the primary research project is to address this gap in knowledge by comprehensively assessing the epidemiology of cancer in NSW farmers.

2.6 Appendix

2.6.1 Protocol for literature review

The following protocol was developed prior to commencing the review and was adapted as necessary. Together with the eligibility criteria, this final version of the protocol version forms a general record of the review method.

- **Types of studies**

A range of observational, epidemiological study designs and reports of studies were considered for inclusion. These consisted of:

- Systematic reviews of observational studies
 - Retrospective and prospective cohort studies
 - Case-control studies
 - Cross-sectional studies
- **Types of participants / characteristics**
 - At least one participant group must either live on or work on a farm
 - The study provides details on how 'farmer' status is defined
 - Cancer diagnoses use ICD classifications
 - Age groups should be specified
 - Settings or regions defined

- **Outcome measures**

Measures of incidence, risk, screening rates, stage of presentation, diagnosis, treatment, outcomes, mortality and survival rates for major cancers in farmers vs. others (all, urban, rural), focusing on the following cancer types:

- Prostate
- Breast
- Colorectal
- Lung
- Melanoma
- Lymphoma
- Myeloma
- Leukaemia

- Electronic searches for identification of studies

Databases searched for identification of studies:

- Medline
- Embase
- BioMed Central
- Informit online
- Cochrane library
- Web of science (kw)
- Scopus
- Google Scholar
- Proquest dissertations and theses
- Hand search of reference lists of primary studies meeting review criteria
- Search strings and databases accessed were recorded.

- Selection of studies

Search results to be merged using Endnote and duplicate records of the same report removed.

- 1st round - Titles and abstracts examined to remove irrelevant reports
- 2nd round - Full-text reports examined for compliance of studies with eligibility criteria.
- Multiple reports of the same study linked.
- Categorised by cancer type for:
 - Incidence/mortality (describing the excess/deficits)
 - Screening, stage of diagnosis, treatment and survival outcomes
- 3rd round - refinement of eligibility criteria

Eligibility criteria for each study were assessed in an established order with the first 'no' response used as the primary reason for exclusion of the study (i.e. remaining criteria not assessed).

- **Data extraction and assessment of potential studies**

A data collection form was devised to assess studies according to set criteria. Assessment of methodological quality of individual studies was guided by:

- The Effective Public Health Practice Project 'Quality Assessment Tool for Quantitative Studies'³
- The 'STROBE statement' guidelines for reporting observational studies²
- Critical Appraisal Skills Programme (CASP) guides for appraisal of cohort studies, case-control studies and reviews⁴

The first and second of these (above), are cited by Cochrane Collaboration Handbook⁵ as useful guides and/or tools for assessing the quality of studies in public health studies. The third assisted in assessing the quality of particular epidemiological study designs. Domains of bias within studies assessed using these tools include selection, performance, detection, attrition and reporting bias.

Whilst farm versus rural versus urban residency and farm occupation/activity are the comparison variables of interest, potential confounders considered in the assessment of bias in studies were age, gender, nationality/race, socio-economic variables (e.g. education, income, marital status), lifestyle factors (e.g. smoking, alcohol, diet, physical activity) and underlying health conditions. However, as it was deemed unlikely that information on most of these would be available, priority consideration was given to control of bias related to age and gender.

- **Measures of exposure effect**

For studies presenting dichotomous data, effect measures for comparison between farmer and non-farmer groups are odds ratio (OR), risk ratio (RR) or risk difference (RD). For continuous data, mean difference (MD) or standardized mean difference (SMD) between groups were assessed.

- **Assessment of heterogeneity and reporting biases**

A diversity of studies was expected and heterogeneity (clinical, methodological and statistical) expected to be high. Meta-analysis was not undertaken. Similar studies were grouped for comparative assessment. Publication bias was minimised by searching eight electronic databases and grey literature sources. Outcomes were not used as criteria for selection, such that significance of results did not affect study selection. Time (year) and language filters were not applied to searches, but were later refined according to study yield for incidence/mortality and risk factor studies - and after systematic review studies were assessed.

- **Data synthesis**

Each study was assessed according to eligibility and quality criteria listed in a data-collection sheet. A narrative summary was produced for each study. Studies were grouped by type, conditions of interest and quality of evidence.

- **Subgroup analysis and summary of findings**

Population subgroups for comparative analyses were: (1) farmer/farm resident; (2) rural non-farmer /non-farm resident; and (3) urban/other. Measures of interest for sub-group analyses were incidence, risk, screening rates, stages of presentation, diagnosis, treatment, outcomes, mortality and survival rates. 'Summary of findings' tables by study type were produced. Cancers of interest were listed, along

with numbers of participants/studies, comparative risk between population subgroups (farmer, rural non-farmer, other) and quality of the overall evidence using the 'GRADE' system.⁴

2.6.2 Eligibility criteria for selection of studies

Eligibility criteria developed to assess review and primary studies are shown in the following tables.

Table 2.1: Eligibility criteria for review studies

1	Addresses objectives of the current review
2	Appropriate studies include reviews of primary cohort, case-control, cross-sectional studies
	Narrative overviews, comments & issues papers not included
	Evaluations of health promotion interventions not included
	Reviews of ecological studies; or qualitative attitudinal & behavioural studies not included
	Reviews with selective reporting of results not included (e.g. reports positive / significant results only)
	Previous versions of studies with updates on same cohort not included in same review
3	Settings, regions specified
4	Details on 'farmer' status provided
	Occupations other than farming NOT included in 'farmer' group
5	Cancer status - diagnoses should use ICD10 classifications, as usually reported by central cancer registries
	Only include those with results for one or more of the 9 cancers of primary interest
6	Incidence and mortality reviews :
	Findings for 3 or more diseases
	Appropriate non-farmer comparison groups
	Both positive & negative OR for several occupations (case-control)
	Component studies age-gender standardised with risk estimates for several cancer sites, elevated & decreased
	Component studies with risk estimates expressed as (SMR), (SIR), (RR), and (HR) in cohort and case-cohort studies, and (OR) in case-control studies.
	Component studies with sufficient data for determining CI
7	Meets threshold of quality using recognised quality appraisal tools
	STROBE ²
	EPHPE ³
	CASP ⁴

Table 2.2: Eligibility criteria for primary studies

1	Addresses objectives of this review
2	Appropriate study design - prospective cohort study - retrospective cohort study - case-control study - cross-sectional studies
3	Settings, regions & age groups specified
4	Farmer status. At least one participant group must either: - Live on a farm - Work on a farm - Details on 'farmer' status provided
5	Occupations other than farming NOT included in 'farmer' group
6	Cancer status - diagnoses should use ICD10 classifications, as usually reported by central cancer registries
7	Meets finer details of inclusion/exclusion criteria: Include: Only those studies with results for one or more of the primary cancers of interest For incidence and mortality studies - only include studies published since 2003 Appropriate non-farmer comparison group Both positive & negative OR for several occupations (case-control) Risk estimates for several cancer sites, elevated & decreased (cohort, mortality studies) Risk estimates expressed as (SMR), (SIR), (RR), and (HR) in cohort and case-cohort studies, and (OR) in case-control studies. Sufficient data for determining relative risk ratios & CI (cohort studies) Confounders adjusted were possible Exclude: For incidence and mortality studies - studies published before 2003 Previous versions of studies with updates on same cohort not included Narrative style & selective reporting of results Evaluations of health promotion interventions Qualitative studies of attitudes & behaviours Farm density/proximity indicator (ecological)
8	Meets threshold of quality using recognised quality appraisal tools - STROBE² - EPHPE³ - CASP⁴

2.6.3 Criteria for assessment of significance and direction of findings in review component studies

Criteria were developed to help standardise and assess the overall direction and strength of findings of component studies and are shown in Table 2.3.

Table 2.3: Criteria for standardising and assessing overall findings for excess or deficit of selected cancer risk in farm compared to non-farm population groups.

Determination for overall review cancer risk = where majority of component studies fall + review conclusion	Incidence or mortality measure of component studies (majority of studies) (PMR, SMR, SIR, OR, RR)		Conclusion
	Value	95% CI	
Clear excess	>1	Minimum limit >1	P<.05 in statistical test
Suggested excess	>1	Minimum >0.97	Narrative statement
No discernible difference	Any	Minimum <0.97 and Maximum >1.03	Narrative statement
Suggested deficit	<1	Maximum <1.03	Narrative statement
Clear deficit	<1	Maximum <1	P<.05 in statistical test

2.6.4 Summary of findings tables for reviews of health service factors

Table 2.4a: Comparison of studies of cancer ‘stage of diagnosis’ and / or ‘treatment’ between farmers and non-farmers

Primary author, year & study title	Setting / what was done / study design F = Farmer AgW = Agricultural worker	No. of farmers / non-farmers	Cancer site	Indicator	% group with indicator / predictor	Statistical measure/ significance (RR, OR / 95% CI or p value)	Quality tool assessment / Overall grading	Key points
Dodge, J. 2007. <i>Cancer survival in California Hispanic farmworkers, 1988-2001</i>	USA (AgW Hispanic) Data-linkage of farm workers union membership & state cancer registry, for Hispanics persons diagnosed with a first malignant tumour. Retrospective cohort study	1,186 / 178,718	Cancer type	Early stage tumor – in situ or localized	% UFW farmworkers: % California Hispanics	UFW farmworkers : California Hispanics RR (95% CI)	EPHPP – Strong STROBE – 2No CASP – 1No Grading: A Impression: Very good	- UFW men were generally diagnosed at an older age and more advanced disease stage than California Hispanics, important for colorectal cancer, which is highly preventable with routine screening. - Compared to California Hispanics, UFW men experienced significantly lower proportions of early-stage diagnoses for all cancer sites combined and screenable colorectal, and prostate cancers. - Women had lower proportions of early stage screenable colorectal and cervical cancers, but not significantly so. No difference for breast cancers. - Conversely, non-Hodgkin’s lymphoma, ovarian, kidney, liver pancreatic cancers were more frequently diagnosed at early tumour stages in UFW versus California Hispanics, but not significantly so.
			All cancers					
			men (m)*		35.1% : 40.7%	RR= 0.86 (0.79 – 0.95) *		
			women (w)		38.0% : 40.5%	RR= 0.94 (0.82 – 1.07)		
			Brain/nervous (m)		56.3% : 68.2%	RR= 0.82 (0.53 – 1.27)		
			Breast		52.4% : 53.2%	RR= 0.99 (0.82 – 1.18)		
			Cervix		44.2% : 50.5%	RR= 0.88 (0.65 – 1.19)		
			Colorectal (m)*		17.4% : 33.7%	RR= 0.52 (0.31 – 0.86)*		
			Colorectal (w)		23.8% : 32.5%	RR= 0.73 (0.34 – 1.58)		
			Corpus uterus		54.5% : 68.1%	RR= 0.80 (0.55 – 1.17)		
			Kidney (m)		55.6% : 46.0%	RR= 1.21 (0.86 – 1.70)		
			Kidney (w)		60.0% : 53.9%	RR= 1.11 (0.67 – 1.85)		
			Larynx (m)		60.0% : 60.9%	RR= 0.99 (0.65 – 1.49)		
			Liver (m)		29.0% : 25.7%	RR= 1.13 (0.65 – 1.97)		
			Lung-bronchial (m)		8.6% : 11.2%	RR= 0.77 (0.39 – 1.49)		
			Lung-bronchial (w)		5.9% : 14.4%	RR= 0.41 (0.06 – 2.74)		
			Melanoma (m)		72.7% : 68.4%	RR= 1.06 (0.73 – 1.53)		
			Myeloma (m)		8.3% : 6.4%	RR= 1.31 (0.20 – 8.62)		
			NHL (m)		35.0% : 25.5%	RR= 1.37 (0.89 – 2.10)		
			NHL (w)		28.6% : 26.0%	RR= 1.10 (0.48 – 2.52)		
			Ovary		33.3% : 19.4%	RR= 1.72 (0.89 – 3.31)		
			Pancreas (m)		8.7% : 6.1%	RR= 1.43 (0.38 – 5.43)		
			Prostate*		56.3% : 69.8%	RR= 0.81 (0.72 – 0.90)*		
			Soft tissue (m)		45.5% : 52.4%	RR= 0.87 (0.45 – 1.66)		
			Stomach (m)		10.2% : 14.4%	RR= 0.71 (0.33 – 1.63)		
			Stomach (w)		13.3% : 17.1%	RR= 0.78 (0.21 – 2.84)		
			Thyroid (w)		57.9% : 57.1%	RR= 1.01 (0.69 – 1.49)		
			Urinary (m)		80.0% : 80.6%	RR= 0.99 (0.83 – 1.19)		

Mills P et al. 2001. <i>Cancer incidence in the United Farmworkers of America (UFW), 1987-1997.</i>	USA (Hispanic farmworkers)			Early-stage tumours: in-situ or localized	% Hispanic UFW farm workers / non-farmers (age adjusted)		EPHPP – Strong STROBE – 5No CASP – 0No	- Hispanic farmworkers union (UFW) men had significantly later stage diagnosis of prostate and colorectal cancers than California Hispanics. - No significant differences in stage of cancer diagnoses for women, in breast, colorectal or cervical cancers.	
	Data-linkage of farm worker union members & California state cancer registry.	68 / 2,126 168 / 1,904 76 / 2,547	Breast Cervical Prostate		55% : 55% 76% : 84% 33% : 64%	RR= 0.99 (0.78 – 1.28) RR= 0.91 (0.80 – 1.03) RR= 0.51 (0.41 – 0.64)* p< .0001*	Grading: A Impression: Very good		
	Retrospective cohort study	49 / 700	Colorectal (m)		12% : 35%	RR= 0.35 (0.16 – 0.75)* p< .01*			
		15 / 583 9 / 96	Colorectal (w) Melanoma (m)		22% : 36% 59% : 82%	RR= 0.55 (0.20 – 1.54) RR= 0.68 (0.37 – 1.22)			
	Desoubeaux N et al. 1997. <i>Social environment and prognosis of colorectal cancer patients: A French population-based study</i>	France (F)	250 / 340, 736, 316	Colorectal	Stage 1: Limited to organ.	% farmers / professionals Men: 43.0% : 48.5% Women: 35.2% : 43.0%			p=0.45 p=0.40
	Colorectal cancer patients diagnosed 1978 - 1987 in Calvados district, France. Cancer registry-based.								
	Retrospective cohort study		Colorectal	Treatment: Surgical resection / other	Men: 78.9% : 78.5% *Women: 68.5% : 81.3%		p=0.76 p=.01*		
McDuffie H et al. 2007 <i>Host factors, occupation, and testicular cancer in Saskatchewan, Canada: 1979-2002</i>	Canada (F)	72 / 349	Testicular	Diagnosis Stage 1, 1A - 1S, A (early stage)	% farmers/ non-farmers 59.7% : 68.8%		RR= 0.88 (0.73 – 1.07) p= 0.2	EPHPP – Moderate STROBE – 2No CASP – 1No	Farmers significantly more likely to be diagnosed with testicular cancer at Stage 2 or above than non-farmers.
	Population-based cancer registry in Saskatchewan.			Regression of variables assoc. with Stage 2 or above	Occupation: ‘farmer’ Age: <26yrs Non-seminoma		OR= 1.76 (1.00 – 3.10)* OR= 2.12 (1.15 – 3.93)* OR= 1.99 (1.30 – 3.31)*	Grading: B Impression: Good	
	Cross-sectional study								

Morshed P et al. 2008. <i>Laryngeal Cancer In Farmers from Lublin Region of Poland.</i>	Poland (F)	84 / 64	Larynx - Laryngeal Squamous Cell Carcinoma	Distribution:			EPHPP – Moderate STROBE – 11N +1 moderate bias CASP – 3No Grading: C Impression: Fair	- Significant differences in presentation pattern - farmers older, more males (unadjusted); and farmers tumours more localised, glottic, more differentiated, suggesting different exposure factors and progress of disease. - Univariate statistical significance for G stage (non-farmers worse) and near significance for N stage (p=0.06) (non-farmers worse) and primary localisation of tumour (p=0.05) (non-farmers supra-glottic). No significant differences in T, M, clinical stage, or smoking / alcohol use.
	Medical record survey of patients with primary laryngeal squamous cell carcinoma diagnosed and treated in Lublin.			T1–T4	ns	p= 0.64		
				N0–N3	ns	p= 0.06		
				M0–M1	ns	p= 0.69		
				G1–G3	*X2=6.23 df=2	p= 0.04		
				Stage I-IV	ns	p= 0.64		
Retrospective cohort study		Stage 1 (early)	% Farmers / non-farmers 17.9%: 15.6%	RR= 1.12 (0.53 – 2.35)				

Note: ns=not significant to .05 level

Table 2.4b: Notes on quality assessment and scoring process for studies of cancer ‘stage of diagnosis’ and / or ‘treatment’

Primary author & year	Study Design	EPHPP ¹ criteria rating	STROBE statement ² : number of 'no' responses & biases	CASP checklist ³ : number of 'no' responses	Combined score	Overall Quality Grading	Overall impression
Dodge 2007	Retro cohort	Strong	2 No	1 No	4	A	Very good
Mills 2001	Retro cohort	Strong	5 No	0 No	4	A	Very good
Desobeaux 1997	Retro cohort	Strong	2 No	0 No	4	A	Very good
McDuffie 2007	Cross-sectional	Moderate	2 No	1 No	6	B	Good
Morshed 2008	Retro cohort	Moderate	11 No + 1 moderate bias	3 No	8	C	Fair
Scoring system		Quality Assessment tools					
Criteria	Score						
Retrospective cohort design	1	EPHPP: Effective Public Health Practice Project criteria ¹					
Cross sectional design	2	STROBE: Strengthening of reporting of Observational Studies in Epidemiology Statement ²					
'In-tool' quality levels (1-3)		CASP: Critical Appraisal Skills Program checklist ³					
Green (normal font)	1						
Yellow (italic font)	2						
Red (bold, italic font)	3						

Table 2.5a: Comparison of cancer ‘survival outcomes’ between farmers and non-farmers

Primary author, year & study title	Setting / what was done / study design F = Farmer AgW = Agricultural worker	No. of farmers / non-farmers	Cancer site	Indicator	Relative % survival	Statistical measure (RR death, OR, Surv, HR) 95% CI or p value	Quality tool assessment / Overall grade	Key results
Eloranta, S. 2010. <i>Does socioeconomic status influence the prospect of cure from colon cancer - A population-based study in Sweden 1965-2000</i>	Sweden (F) Occupation-based SES assessment of all persons with colon cancer in national cancer registry 1965-2000. Retrospective cohort study.	5,902 / 3,479 19,878 5,044 24,570	Colorectal	Excess mortality (RR death)	-	Farmers: Higher non-manual workers RR death 1.18 (1.11 – 1.26)* (RR near 1.50 within 6 months of diagnosis, then near parity after)	EPHPP – Strong STROBE – 2No CASP – 0No Grading: A Impression: Very good	- Farmers assessed as one of 5 SES groups- higher non-manual workers, self-employed, manual workers and lower non-manual workers. - Farmers had the highest excess mortality, most pronounced within 6 months of diagnosis. Farmers had the lowest odds of cure. All lower SES groups had similar but lower survival than the referent group (higher non manual workers). - Confounder adjusted results suggest SES differences cannot be attributed solely to lead time bias.
Dodge, J. 2007. <i>Cancer survival in California Hispanic farmworkers, 1988-2001</i>	USA (Agw Hispanic) Data-linkage of farm workers union membership & state cancer registry, for Hispanics persons diagnosed with a first malignant tumour. Retrospective cohort study	1,186 / 178,718	Cancer type	5 Year survival (observed)	% UFW farm-workers: California Hispanics	p value	EPHPP – Strong STROBE – 2No CASP – 1No Grading: A Impression: Very good	- Crude 5-year cancer-specific survival rates were lower for Hispanic UFWA men compared to California Hispanic men for all cancer sites combined and colorectal cancer and higher for non-Hodgkin's lymphoma. - Only non-Hodgkin's lymphoma survival differences were significant after adjusting for age and stage at diagnosis. UFW men had a 66% decreased risk of death from non-Hodgkin's lymphoma compared to California Hispanic men in the adjusted model. - No statistically significant survival
			All cancers					
			men (m)		53.7% : 57.7%	p= 0.02*		
			women (w)		61.1% : 61.5%	p= 0.91		
			Brain/nervous (m)		39.8% : 37.3%	p= 0.77		
			Breast		77.2% : 81.6%	p= 0.63		
			Cervix		73.0% : 78.5%	p= 0.38		
			Colorectal (m)		48.1% : 60.6%	p= 0.01*		
			Colorectal (w)		64.9% : 61.3%	p= 0.99		
			Corpus uterus		90.2% : 92.5%	p= 0.61		
			Kidney (m)		80.8% : 61.5%	p= 0.17		
			Kidney (w)		64.3% : 68.2%	p= 0.67		

						Larynx (m) Leukaemia (m) Leukaemia (w) Liver (m) Lung-bronchial (m) Lung-bronchial (w) Melanoma (m) Myeloma (m) NHL (m) NHL (w) Ovary Pancreas (m) Prostate Soft tissue (m) Stomach (m) Stomach (w) Thyroid (w) Urinary (m)	78.6% : 75.9% 29.3% : 42.2% 44.4% : 40.1% 21.1% : 22.1% 12.4% : 13.9% 25.8% : 18.8% 66.7% : 74.8% 38.6% : 36.5% 86.7% : 57.6% 82.5% : 62.7% 58.7% : 49.4% 0.0% : 6.6% 87.8% : 88.3% 88.9% : 71.6% 10.6% : 26.1% 21.8% : 27.4% 100% : 95.5% 88.1% : 82.9%	p= 0.52 p= 0.33 p= 0.76 p= 0.76 p= 0.16 p= 0.71 p= 0.87 p= 0.96 p= 0.01* p= 0.38 p= 0.63 p= 0.99 p= 0.59 p= 0.65 p= 0.27 p= 0.82 p= 0.38 p= 0.25	UFW farmworkers : California Hispanics / HR (death) adjusted age & stage / (95% CI)	differences were detected between United Farm Workers of America and California Hispanic women.
						Breast Cervix Colorectal (m) Colorectal (w) Lung-bronchial (m) Lung-bronchial (w) NHL (m) Prostate	- - - - - - - -	HR= 1.14 (0.73 – 1.79) HR= 1.15 (0.65 – 2.03) HR= 1.35 (0.93 – 1.95) HR= 1.01 (0.45 – 2.24) HR= 1.09 (0.86 – 1.40) HR= 0.81 (0.42 – 1.55) HR= 0.34 (0.14 – 0.81)* p =.02* HR= 0.75 (0.51 – 1.11)		
Desoubreaux N et al. 1997. <i>Social environment and prognosis of colorectal cancer patients: A French population-based study</i>	France (F) Colorectal cancer patients diagnosed 1978 - 1987 in Calvados district, France. Cancer registry-based. Retrospective cohort study	250 / 340	Colorectal	5 year survival	% farmers : Men: 30.6% : 42.9%	RR death farmers : professionals RR death (adj. for age, stage & treatment) RR= 1.44 (1.02 –2.03)*	EPHPP – Strong STROBE – 2No CASP – 0No Grading: A Impression: Very good	- Poorer prognosis among farmer group for both genders compared to higher social-professional group (managerial, teaching and self-employed people). - Differences not explained by variations in tumour stage at diagnosis or in treatment alone, or by potential		

					Women: 27.0% : 48.2%	RR death (adj. for age, stage & treatment) RR= 1.94 (1.26 – 3.00)*		variations in co-morbidity associated with sex and age (adj for confounders)
Morshed P et al. 2008. <i>Laryngeal Cancer In Farmers from Lublin Region of Poland.</i>	Poland (F) Medical record survey of patients with primary laryngeal squamous cell carcinoma diagnosed/ treated in Lublin. Retrospective cohort study	84 / 64	Larynx-Laryngeal Squamous Cell Carcinoma	3 year survival 5 year survival	% farmers : non-farmers 64.2% : 73.4% 42.9% : 56.3%	RR death farmers : non- farmers p=0.97 RR death= 1.08 (0.80 – 1.46) p=0.78 RR death= 1.20 (0.82 – 1.75)	EPHPP – Moderate STROBE – 11No +1 moderate bias CASP – 3No Grading: C Impression: Fair	For laryngeal cancer (LSCC), the 3-year and 5-year survival rate in farmers was slightly lower than non-farmers, but this difference and relative risk of death between groups was not statistically significant.
Vagero et al 1987. <i>Cancer survival and social class in Sweden</i>	Sweden (F) Survival analysis of national cancer registrants 1961-1979 by social- occupational groupings. Retrospective cohort study	4936 / 17661, 36763 (men)	Cancer type (men only) All cancers Bladder Colon Kidney Lung Pancreas Prostate Rectum Stomach Testes	5 Year survival probability	Estimated probability (eyeball) from survival curves Farm-men: white collar men est. 0.39: 0.42 est. 0.71: 0.73 est. 0.37: 0.48 est. 0.40: 0.48 est. 0.12: 0.10 est. 0.03: 0.01 est. 0.49: 0.55 est. 0.32: 0.48 est. 0.14: 0.13 est. 0.62: 0.76	Text description of survival probability: Farm men < white collar Farm men < white collar Farm men < white collar Farm men < white collar No real difference No real difference Farm men < white collar Farm men < white collar No real difference Farm men < white collar	EPHPP – Moderate STROBE – 10N +2 moderate biases CASP – 3No Grading: C Impression: Fair – some reporting issues	- There was a higher survival probability for white collar men than for blue collar men or self-employed farm men for all cancer, cancer of the colon, rectum, kidney, bladder, prostate & testes. For lung cancer, cancer of the stomach, and pancreatic cancer there were no detectable differences in survival probability. *NB. No tests of significance reported, No adjustment for confounders. Text description and 'eyeball' graphs of results presented only. Difficult to draw firm conclusions from the data.

Table 2.5b: Notes on quality assessment and scoring process for studies of cancer studies of survival outcomes

Primary author & year	Study Design	EPHPP ¹ criteria rating	STROBE statement ² : number of 'no' responses & biases	CASP checklist ³ : number of 'no' responses	EPHPP ¹ criteria rating	Overall Quality Grading	Overall impression
Eloranta 2010	Retro cohort	Strong	2 No	0 No	4	A	Very good
Dodge 2007	Retro cohort	Strong	2 No	1 No	4	A	Very good
Desobeaux 1997	Retro cohort	Strong	2 No	0 No	4	A	Very good
Morshed 2008	Retro cohort	Moderate	11 No + 1 moderate bias	3 No	8	C	Fair
Vagero 1987	Retro cohort	Moderate	10 No + 2 moderate bias	3 No	9	C	Fair
Scoring system		Quality Assessment tools					
Criteria	Score						
Retrospective cohort design	1	EPHPP: Effective Public Health Practice Project criteria ¹					
Cross sectional design	2	STROBE: Strengthening of reporting of Observational Studies in Epidemiology Statement ²					
'In-tool' quality levels (1-3)		CASP: Critical Appraisal Skills Program checklist ³					
Green (normal font)	1						
Yellow (italic font)	2						
Red (bold, italic font)	3						

Table 2.6a: Comparison of studies of cancer screening between farmers and non-farmers

Primary author, year & study title	Setting / what was done / study design F = Farmer AgW = Agricultural worker	No. of farmers / non-farmers	Cancer type screened	Indicator	% group with indicator/predictor	Statistical measure (RR, OR, HR) 95% CI or p value	Quality tool assessment / Overall grade	Key results
Park H et al. 2002. <i>Health risk factors among Iowa farmers</i>	USA (F) Compared prevalence of health risks among farmers and other workers from Computer Assisted Telephone Interviews as part of Iowa Behavioural Risk Factor Surveillance System Cross-sectional study	2140 (all). No. in farm / non-farm groups not reported	Any	Routine check-up	% Farmers: non-farmers	OR adjusted for sex, age, school, marital status	EPHPP – Moderate STROBE – 6No CASP – 1No Grading: B Impression: Good	- Most health conditions, risk factors and screening behaviours were similar among farmers and other workers. - Farmers were less likely to have had stool blood screening (FOBT) for colorectal cancer in the past year. - There was no difference in screening between groups for breast or cervical cancer.
				(past year) (1 yr+ ago)	Not reported	OR= 0.72 (0.17 – 3.07) OR= 0.99 (0.29 – 3.43)		
			Colorectal	Faecal Occult Blood Test (FOBT) (past yr) (> 1 yr ago)	Not reported	OR= 0.41 (0.17 – 1.00)* OR= 1.33 (0.63 – 2.79)		
				Sigmoidoscopy (past yr) (> 1 yr)	Not reported	OR= 1.44 (0.59 – 3.52) OR= 0.77 (0.36 – 1.66)		
			Breast	Mammogram (past yr) (> 1 yr)	Not reported	OR= 1.22 (0.14 – 10.52) OR= 0.79 (0.06 – 11.03)		
				Clinical breast exam (past yr) (> 1 yr)	Not reported	OR= 0.80 (0.09 – 7.09) OR= 0.80 (0.05 – 12.60)		
			Cervical	Pap test (past yr) (> 1 yr)	Not reported	OR= 0.57 (0.06 – 5.03) OR= 0.78 (0.06 – 9.73)		

Muldoon J et al. 1996 <i>Utilization of cancer early detection services among farm and rural nonfarm adults in Iowa.</i>	USA (F)	1126 / 1092	Any	Primary care checkup in last 12 months	% Farm: % non- farm		EPHPP – Moderate STROBE – 1No CASP – 0 No Grading: B Impression: Good	- Farmer group older on average and less likely to have preventive health services covered by health insurance. - Farm men were less likely to have had a check-up during the past year, but no difference for women. - Overall differences in screening behaviours were small. - Farm women 40-49 yrs more likely to have mammogram in past 2 yrs, but the more non-farm women over 50yrs had mammogram in past year. - No difference between farmers and non-farmers for breast examinations or for Pap tests - Farmers over 50yrs less likely to have had a prostate examination - No difference in groups for FOBT for men or women, but farm women more likely to have a sigmoidoscopy. - Farmers more likely to have had a skin examination. - Controlling for demographic characteristics (age, income) and health insurance coverage, farm and rural nonfarm population were equally likely to use multiple screening according to approved guidelines.		
	Home interviews of farm and non-farm rural residents comparing use of cancer early detection services using Behavioural Risk Factor Surveillance System and National Health Interview Survey items.	Preventive care covered by insurance	Men:	33.5% : 45.6%	OR= 0.60 (0.47 – 0.77)*					
			Women:	52.4% : 56.8%	OR= 0.84 (0.66 – 1.06)					
			Men:	59.6% : 74.9%	OR= 0.49 (0.36 – 0.67)*					
			Cross-sectional study	Breast	Clinical Breast Exams	Women:			62.4% : 75.5%	OR= 0.54 (0.40 – 0.72)*
					Age 40+ (past year)	53.8% : 53.7%			OR= 1.00 (0.78 – 1.28)	
	Mammogram 40-49 yrs (past 2 yrs)	63.3% : 49.8%			OR= 1.74 (1.16 – 2.61)*					
	50 yrs + (past year)	42.2% : 54.3%	OR= 0.62 (0.45 – 0.84)*							
	Monthly Breast self-exam	48.2% : 51.8%	OR= 0.92 (0.73 – 1.17)							
	Cervical	Pap Test (past 3 yrs)	78.0% : 79.0%	OR 0.95 (0.71 – 1.26)						
	Prostate	Prostate exam (past year)	40yrs +	34.5% : 38.1%	OR= 0.86 (0.65 – 1.13)					
			50yrs +	40.7% : 49.3%	OR= 0.70 (0.50 – 0.99)*					
	Colorectal	Faecal Occult Blood Test	Men	16.7% : 17.8%	OR= 0.93 (0.62 – 1.90)					

				Women		
				20.2 % : 20.3%	OR= 1.00 (0.68 – 1.47)	
				Sigmoidoscopy		
				50yrs+		
				(past 5 yrs)		
				Men	OR= 0.92 (0.67 – 1.45)	
				21.5% : 21.8%		
				Women		
				23.7 % : 15.9%	OR= 1.64 (1.07 – 2.54)*	
Skin				Skin exam		
				(past year)		
				40yrs+		
				Men	OR= 1.70 (1.16 – 2.50)*	
				Women		
				12.9% : 6.7%	OR= 2.05 (1.33 – 3.16)*	
				50yrs+		
				Men	OR= 1.49 (0.96 – 2.31)	
				Women		
				13.9% : 8.6%	OR= 1.71 (1.02 – 2.87)*	
Combined skin/prostate/ Colorectal				Multiple		
				Tests (50yrs+)		
				Skin & prostate	None of 4	
				exam / FOBT &	recommended	
				Sigmoidoscopy	tests	
				screening (per		
				recommended	Men	
				guidelines)	51.2% : 45.4%	ns
					Women	
					11.5% : 10.3%	ns
				Regression on		
				variables	Men:	
				associated with	Farmers /	
				non-compliance	non- farmers	
				with screening		
				guidelines	Income	ns
					Education	ns
					Increasing age	ns
					(per year)	
					No preventive	
					care health	
					OR= 0.94 (0.93 – 0.97)*	

					insurance				
					Women:				
					Farmers / non- farmers				
					Age	OR= 0.68 (0.50 – 0.97)*			
					Education	ns			
					No preventive care health insurance	ns			
					Income:	OR= 0.46 (0.23 – 0.91)*			
					<\$15,000	OR= 0.37 (0.04 – 2.33)*			
					\$15–50,000	OR= 0.11 (0.01 – 0.86)*			
McCarty, C. 2003 <i>Differences in preventive screening rates in Wisconsin farm and non-farm resident women</i>	USA (F)	675 / 825	Cervical	Regression predictors for Pap test in last 3 yrs	Non-f arm residence	OR= 0.75 (0.59 – 0.96)*	EPHPP – Moderate STROBE – 9 No + 1 moderate bias CASP – 2 No	- 3.7% of rural women had never had a Pap test, and 19.3% of women 40 yrs+ had never had a mammogram. - Age was inversely related to Pap tests and positively correlated with mammograms - (?) “Farm residents were significantly less likely to have Pap tests” at recommended time intervals (contradicts the results table) - Farm women reported health insurance a problem, but health insurance did not affect mammogram screening rates	
					Age (per yr)	OR= 0.97 (0.96 – 0.98)* p<.05			
					Health insurance a problem	OR= 0.94 (0.72 – 1.21)	Grade: C Impression: Fair		
			Breast	Regression predictors for mammogram last 2 yrs (40yrs+)	Non-farm residence	OR= 0.73 (0.53 – 1.02)			
		Age (per yr)			OR= 1.04 (1.02 – 1.06)* p< .05				
					Health insurance a problem	OR= 0.75 (0.53 – 1.05)			
			Both / any	Reported Health insurance a problem for preventive screening					
					% Farm: non-farm women 43.9% : 21.7%	p< .001*			

Kakefuda I 2006 <i>Comparisons of Colorado women's cancer screening practices by residence: Metropolitan, non-metropolitan, and farm</i>	USA (F) Compared screening practices of metropolitan and rural women interviewed in state-based or farm-based surveys Cross-sectional study	299 / 956	Cervical	Recent Pap test (past year)	63.2%: 61.2% : 67.1%	ns	EPHPP – Weak STROBE – 1 No + 2 moderate biases CASP – 1No Grading: C Impression: Fair	- Farm women were more likely to be white, older, report their health as very good, have medical insurance than other rural women, which influenced screening. - After controlling for related variables, residence was not associated with the screening practices, except farm women were less likely to have a recent breast examination than metropolitan women. When non-metropolitan and farm women were combined, there was no association between residence and having had a physical breast examination. - Some sampling issues
				Regression on variables assoc. with NOT having Pap test in past year	Farm residence Race/ethnicity Marital status General health Financial Age groups over 30yrs Education: Incomplete High school Incomplete College grad No medical insurance No primary medical care place	ns OR 1.41 (0.96 – 2.08) ns ns ns ns OR> 1.71 (1.02 – 2.86)* OR> 1.96 (1.02 – 3.79)* OR> 1.89 (1.30 – 2.75)* OR= 1.86 (1.11 – 3.11)* OR= 5.28 (2.99 – 9.34)*		
				Breast	Mammogram (past 2 yrs) 40 yrs+	73.7%: 62.0%: 73.9%	ns	
					All ages	62.2%: 44.7%: 51.63%	p< .01*	
					Regression on variables assoc. with NOT having mammogram in past 2 yrs	Farm residence Race/ethnicity Marital status General health Financial Age < 30yrs Education < College grad	ns OR= 1.15 (0.08 – 1.66) ns ns ns ns OR> 7.49 (5.11 – 10.97)* OR> 1.66 (1.15 – 2.39)*	

					No medical insurance	OR= 2.74 (1.58 – 4.76)*			
					No primary medical place	OR= 4.97 (2.62 – 9.44)*			
					Breast examination (past year)				
					40 yrs+	64.6%: 66.0%: 69.3%	ns		
					All ages	67.2%: 64.2%: 69.2%	ns		
					Regression on variables assoc. with NOT having exam in past year	Race/ethnicity	ns		
						General health	ns		
						Age	ns		
						Farm residence	OR= 1.50 (1.07 – 2.10)*		
						Marital status	OR= 1.38 (1.03 – 1.86)*		
						Financial	OR= 1.77 (1.15 – 2.74)*		
						Education:			
						<High school graduation	OR= 2.20 (1.31 – 3.70)*		
						No medical insurance	OR= 1.81 (1.16 – 2.82)*		
						No primary medical care place	OR= 5.27 (3.17 – 8.73)*		
Carruth A. 2006. <i>The impact of farm lifestyle and health characteristics: cervical cancer screening among southern farmwomen</i>	USA (F)	2324 / No. of non-farmers not reported	Cervical	Failure to obtain Pap test in past 3 yrs in:	Farm women crude failure rate % : State adjusted failure rate %	95%CI for % failure rate	EPHPP – Weak STROBE – 5 No + 1 moderate bias CASP – 3 No	- Failure of farm women to obtain cervical cancer screening in Texas was comparable to state BRFSS rates, but significantly greater in the other states. Failure rates for farm women were at least 6% greater in Kentucky and 12% greater in Louisiana than state failure rates. - Farm lifestyle predicting failure to obtain cervical cancer screening were	
	Compared predictors for and proportion of farmwomen >or=18 yrs who failed to obtain a Pap test within the past 3 years, within Computer Assisted Telephone Interviews Behavioural			Texas	Farmers 19.6% State 19.6%	(15.6 – 22.6) (16.3 – 22.9)	Grading: D Impression: Fair		
				Louisiana	Farmers 27.9% State 15.2%	(24.5 – 31.3)* (12.3 – 18.1)			

Risk Factor Surveillance System data for Kentucky, Texas and Louisiana.	Cross-sectional study	Kentucky	Farmers	26.8%	(23.9 – 29.4)*	having a house on the farm, engaging in no off-farm work and minimal involvement in farm tasks. - Failure increased with age & lack of insurance. Failure decreased with education, previous mammogram or breast examination & being married. - Time to health facility was ns, although social-geographic isolation and minimal role involvement on the farm may contribute to the likelihood women do not seek cervical cancer screening. – Some comparison issues
			State	20.5%	(17.8 – 23.2)	
			Farmer group only: regression on variables associated with failure to obtain: Pap test in last 3 yrs	Home on farm	OR= 1.78 (1.32 – 2.38)*	
				Role – no off-farm work. & <7 farm tasks	OR= 1.74 (1.00 – 3.20)*	
				Education	OR= 1.99 (1.46 – 2.69)*	
				< High school	OR= 1.51 (1.78 – 1.93)*	
				High school		
				Age		
				40-49 yrs	OR= 3.01 (1.90 – 4.77)*	
				50-59 yrs	OR= 4.01 (2.55 – 6.33)*	
Rosenman K 1995. <i>U.S. farm women's participation in breast cancer screening practices</i>	USA (F)	680 / (secondary data source)	Breast	% Farm:	EPHPP – Weak	- Farm women in this survey had breast cancer screening at rates similar to or above those in the general population. (But significance levels not reported & are unlikely to be). - Mammogram usage increased with higher education, income, and insurance coverage and decreased in women age 75 years or older - Because of a limited response rate (63.5%) and the relative affluence of the farming community in these 4 counties, results are probably not generalizable to all populations of farm
				% State	STROBE – 12 No	
				(secondary data source)	+ 3 moderate biases	
					CASP – 5 No	
				Clinical breast exam:	Grade E:	
				Past year	Impression: Poor	
				Past 3yrs		
				Ever		
				66.6%: -		
				86.2%: -		
Cross-sectional baseline survey	USA (F)	680 / (secondary data source)	Breast	88.1%: -		- Farm women in this survey had breast cancer screening at rates similar to or above those in the general population. (But significance levels not reported & are unlikely to be). - Mammogram usage increased with higher education, income, and insurance coverage and decreased in women age 75 years or older - Because of a limited response rate (63.5%) and the relative affluence of the farming community in these 4 counties, results are probably not generalizable to all populations of farm
				Mammogram (40yrs+):		
				Past year	51.9%: -	

	Past 3yrs Ever	73.7%: - 80.6%: 74.3%	sig not reported	or rural women. – sampling issues & indirect comparisons to secondary data
	(50yrs+): Past year	62.4%: 57.9%	sig not reported	
	Farm group only: Regression on variables assoc. with mammo- gram (40yrs+) in past 3 years	Age (ref 40-49) 50-74yrs 75yrs+ Insurance (ref none) low high Education (ref < High school) College High school Income (ref < \$25,000) \$25 – 50,000 > \$50,000	OR> 2.46 (1.27 – 4.73)* ns OR= 4.48 (2.26 – 8.86)* ns OR= 2.12 (1.10 – 4.08)* ns OR= 1.92 (1.17 – 3.14)* ns	

Note: ns=not significant to .05 level

Table 2.6b: Quality assessment and scoring of studies of cancer screening between farmers and non-farmers.

Primary author & year	Study Design	EPHPP ¹ criteria rating	STROBE statement ² : number of 'no' responses & biases	CASP checklist ³ : number of 'no' responses	Combined score	Overall Quality Grading	Overall impression
Park 2002	Cross-sectional	<i>Moderate</i>	6 No	1 No	6	B	Good
Muldoon 1996	Cross-sectional	<i>Moderate</i>	1 No	0 No	6	B	Good
McCarty 2003	Cross-sectional	<i>Moderate</i>	9 No + 1 moderate bias	2 No	8	C	Fair
Kakefuda 2006	Cross-sectional	Weak	1 No + 2 moderate bias	1 No	9	C	Fair
Carruth 2006	Cross-sectional	Weak	5 No + 1 moderate bias	3 No	10	D	Fair
Roseman 1995	Cross-sectional	Weak	12 No + 3 moderate bias	5 No	11	E	Poor

Scoring system		Quality Assessment tools	
Criteria	Score		
Retrospective cohort design	1	EPHPP: Effective Public Health Practice Project criteria ¹	
Cross sectional design	2	STROBE: Strengthening of reporting of Observational Studies in Epidemiology Statement ²	
'In-tool' quality levels (1-3)		CASP: Critical Appraisal Skills Program checklist ³	
Green (normal font)	1		
Yellow (italic font)	2		
Red (bold, italic font)	3		

Footnotes to Tables:

1. Effective Public Health Practice Project: Quality Assessment Tool for Quantitative Studies. . Hamilton, Ontario: McMaster University; 2010.
2. Elm E AD, Egger M, Pocock S, Gotsche P and Vanderbrouke J: The strengthening of reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of Clinical Epidemiology 2008, 61:344-349.
3. Public Health Resource Unit. Critical Appraisal Skills Programme (CASP) England Public Health Resource Unit, England 2006.

Article: A review of prostate cancer incidence and mortality studies of farmers and non-farmers, 2002-2013: Publication 1.

Appendix item 2.6.5

This manuscript that was published in *Cancer Epidemiology* in December 2014

Depczynski J, Lower T. **A review of prostate cancer incidence and mortality studies of farmers and non-farmers, 2002-2013.** *Cancer Epidemiology* 2014, **38**(6):654-662.

2.6.5.1 Abstract

Objectives: To review the recent literature on the incidence and mortality of prostate cancer in farmers compared to non-farmers. *Methods:* Searches were conducted in seven electronic databases for observational studies published from 2002-2013. Studies were assessed against eligibility criteria and a narrative summary of findings presented. *Results:* Eighteen primary research articles were included in the review. Four of ten mortality studies and two of nine incidence studies reported statistically significant increases in prostate cancer risk in farmers. However, nearly half of all studies reported non-significant reductions in farmers' risk. Additionally, one study reported significantly increased and decreased risk using different outcome measures. Results varied considerably by geographic region, study design and degree of control for confounders, affecting comparability and strength of findings. *Conclusions:* The overall evidence for increased prostate cancer risk in farmers was weak.

Keywords: prostate cancer; farmer; agricultural worker; incidence; mortality

2.6.5.2 Introduction

Prostate cancer is the most frequently diagnosed cancer in men in the developed world.⁴⁷ It is commonly diagnosed as result of Prostate Specific Antigen (PSA) screening and generally progresses more slowly than other cancers. Nonetheless, it is the second most common cause of cancer death in Australia (2011),⁴⁷ Britain (2011)⁴⁸ and the United States (2009);⁴⁹ and third most common in Canada (2008),⁵⁰ the European Union (2009)⁵¹ and New Zealand (2010).⁵²

There has been ongoing interest in the possibility that pesticide and other agricultural exposures may be related to a higher risk of prostate and other cancers.^{9, 11, 32, 53} Farmers are exposed to a range of potential chemical and biological carcinogens in the course of their work, so studies on cancer risk in farmers were considered useful for informing safe work practices; as well as for providing insights into development of cancers in the general population.^{9, 32} As a potentially high risk occupational group, they were the focus of a number of reviews on cancer risk in the latter part of the 20th Century.^{7, 9, 15, 27, 32, 54-55}

One third of 28 studies reviewed in 1996 found statistically significant increases in prostate cancer mortality in farmers compared to non-farmers.²⁷ Three meta-analyses published between 1997 and 2003 also reported increased prostate cancer rate ratios in farmers (1.07 -1.13). However, results have varied considerably by study design, outcome measures used and geographical location.^{7, 15, 54} Previous reviews noted that pooled rate ratios of risk for European studies tend to be lower than for American studies;^{7, 54} and meta-ratios for Standardised Mortality Rates or Ratios (SMR) were not significant in contrast to increased risk in studies that used Proportionate Mortality Ratios (PMR). One review suggested that the broad range of study methods and findings in the past, provide limited usefulness for assessing carcinogenic exposures.⁷ Others propose that elevated cancer risk in farmers may be related to lifestyle factors or pesticide exposures, but this remains unclear.^{7, 15, 27, 54}

In recent years, better information on farm exposures has enabled more research on associations between cancer and particular pesticide products.^{53, 55-57} Important as these developments are, it has been suggested that pesticides are not likely to explain observed cancer patterns in farmers.¹¹ Either way, monitoring the incidence and mortality of cancer in farmers over time, may well assist safety authorities assess progress toward reducing potentially harmful occupational exposures; or provide insight on other directions for research.

The aim of this review is to compare the incidence and mortality of prostate cancer in farmers and non-farmers in more recent studies. Only studies published after January 2002 were considered, thereby excluding studies already incorporated into previous reviews and meta-analyses.^{7, 10, 15, 27, 54}

Studies were restricted to countries classified as 'very highly developed', based on the 2010 United Nations Human Development Index (UN HDI).⁶ This was to enable comparison with findings of earlier reviews which also focused on advanced economies; but also to assess risk for cohorts operating within similar agricultural systems. That is, whilst farming operations will vary with the commodity produced (e.g. wool, grains), it is proposed that it is the level of economic development that is more likely to differentiate the tasks, experience and potential cancer risks of subsistence farmers in the developing world, from the commercial farmer cohorts of advanced economies. The latter were considered more comparable regarding farming practices, financial capacity, access to health services and legislated safety standards (e.g. regarding pesticides). It is not to suggest that by exclusion the cancer experience of farmers in less developed countries is any less important, or could not be the subject of parallel analysis.

2.6.5.3 Methods

The eligibility criteria for studies included in the review are listed below.

- Studies were restricted to publication between January 2002 and December 2013.

- Study designs included were prospective and retrospective cohort studies, case-control studies and cross-sectional studies. Excluded designs were clinical or biomedical studies focusing on cures and treatments; evaluations of health promotion interventions; qualitative studies of attitudes and behaviours; reviews, overviews and selective reports summarising other studies; and ecological studies where exposure measures are based on farm density/proximity indicators.
- Populations of study were located within the 42 countries with 'very high human development' listed in the UN HDI index (2010).
- Farmers were defined by residential status (living on a farm), by occupational listing or by membership of a relevant association or registry. Where not described, 'farming' was considered to mean performance of agricultural operations to grow crops or raise livestock. Comparison groups were adequately described to ensure 'non-farmer' status.
- Occupations other than farming were NOT included in the 'farmer' group, with the exception of 'agricultural pesticide applicators' where they are not differentiated from farmers. Forestry and fishery workers were not considered to be farmers in the general sense of the term, nor included in farmer groups.
- Risk factor studies, health service utilisation studies and those that did not include specific data on prostate cancer incidence or mortality in farmers, were not included.
- Outcome measures considered were standardised mortality rate or ratio (SMR), relative standardised mortality ratio (rSMR), standardised incidence rate or ratio (SIR), proportionate mortality ratio (PMR), odds ratio (OR), hazard ratio (HR), relative risk or risk ratio (RR). The seldom used 'rSMR' was defined as a calculation of the SMR for each cause relative to the SMR for all other causes.⁵⁸ Studies were required to report 95% confidence intervals to be considered for inclusion.
- Cancer diagnoses based on ICD9 or ICD10 classifications.

- Research articles were not included if updates on the same cohort were published in later years.

Searches for English language abstracts were conducted on Web of Knowledge (Medline), Biomed Central, Scopus, Embase, Informit, Google Scholar and Proquest Dissertations & Theses. Search concepts and terms used in databases were: (1) Farm* or Agricultur* or occupation*; AND (2) (cancer OR melanoma OR lymphoma); AND (3) (incidence OR presentation OR diagnosis OR treatment OR screening OR mortality OR death OR survival OR risk). These were adapted for each search tool as required and were confined to appearance in the title or abstract, so that cancer and 'farming' or 'occupation' were the focus of the research. The search was limited to the 12 calendar year period from 2002 to 2013 and was inclusive of all major cancer groupings and 'risk factors'. This was done to ensure articles with a slightly different focus that included information about prostate cancer risk, were also considered.

Search results were collated and merged using Endnote[®] X3 with duplicate records removed. Titles and abstracts were initially examined to remove any obviously irrelevant articles, such as commentaries or case studies. Potentially eligible full-text articles were retrieved and examined for compliance with the criteria.

All study papers identified by the principal researcher as meeting the inclusion criteria were subsequently assessed by a second researcher against the eligibility criteria. Additionally, for studies defined by the principal researcher as not meeting the criteria for inclusion, abstracts were read and classified independently by the second researcher. Where there was disagreement on the classification, further investigation of the relevant papers and discussion between the two researchers resolved the assessment.

A meta-analysis was not performed, as only a small number of eligible studies were retrieved and these assessed a variety of outcome measures. Individual studies were appraised with reference to the 'Strobe' Statement for quality reporting of observational studies and two recognised appraisal tools.²⁻⁴ These tools were used to guide development of the eligibility criteria and summary tables, which were ordered by mortality/incidence measures and geographic region.

Identification and control of potential confounders was considered a measure of study quality and noted accordingly. Whilst the 'GRADE' system was initially considered in assessing quality of evidence across studies, this was later deemed inappropriate for a review of observational studies, as the 'quality of evidence' from such studies is usually classified as 'LOW'.⁵ Therefore, a narrative summary of the strength of evidence for differences in prostate cancer risk between farmers and non-farmers is provided.

2.6.5.4 Results

A total of 2241 abstracts were retrieved for the defined publication period. Duplicate articles, and those with ineligible study groups or designs, were excluded (n=1773). This included 34 studies of cohorts not within 'very highly developed nations' and left 468 full-text primary research articles for further scrutiny.⁶

Risk factor studies (n=194) and health service related studies (n=31) that did not include data on incidence or mortality were further excluded. Studies that did not include specific information on prostate cancer in farmers, or did not report levels of statistical significance or confidence intervals, were also excluded (n=225). This left 18 primary articles for inclusion, of which nine reported on farmers' prostate cancer mortality, eight reported on incidence and one reported on both prostate cancer mortality and incidence. The final search was completed in February 2014.

- *Mortality*

A total of ten studies reported on differences in prostate cancer mortality between farmers and non-farmers (Table 2.7).

Table 2.7: Published studies reporting on differences in prostate cancer mortality between farmers and non-farmer groups (January 2002- December 2013)

Primary author, year, title of study	Country Farm occupational sub-categories	Study design	Study summary	Total farmers in cohort (+/- cases : controls)	Non-farmer comparison group	No. farmer deaths	Outcome measure	Rate ratio (95% CI)	Limitations
European studies									
Frost et al 2011.	United Kingdom Agricultural workers, Pesticide applicators ¹	Retrospective cohort study	Rates for working age farmers who were certified agricultural pesticide users in the UK (1987- 2004)	62,960	Rest of UK population	33	SMR	0.80 (0.57, 1.12)	- unclear if commercial pesticide applicators are included - ratio based on small number of cancer deaths
Office of National Statistics 2009	United Kingdom Farmers, Agricultural workers	Retrospective cohort study	Ratios for all occupations from death certificates for those aged 16-74 years (1991-2000).	Not reported	UK All other occupations	1,177	PMR	1.14 (1.08, 1.21)*	- no separation of farmers vs. agricultural workers - based on last occupation - selective presentation of results for many occupations and diseases - limited discussion on the prostate cancer
Mastrangelo et al 2005	Italy Dairy farmers	Retrospective cohort study	Rates for major cancers in Italian dairy farmers 14 yrs & over (1970-1998)	2,561	Veneto regional population, Italy	16	SMR	0.69 (0.39, 1.15)	- ratio based on small number of cancer deaths
Bucchi et al 2004	Italy Farmers, Agricultural workers	Retrospective cohort study	Rates for farmers & agricultural workers (all ages) from the Forli region in Italy (1969-1993)	36,579	Forli regional population, Italy	293	SMR	0.94 (0.76, 1.16)	- no separation of farmers vs. agricultural workers

Non European studies									
Fragar et al 2011	Australia Farmers, Farm managers	Retrospective cohort study	Rates for farmers & farm managers aged 25-75yrs (1999- 2002)	124,010 ⁴	Australian population	200	SMR	2.40 (1.70, 3.28)*	- limited discussion on findings (short report)
Waggoner et al 2011	USA Farmers, Pesticide applicators ²	Prospective cohort study	Rates for working age farmers / pesticide applicators (1993- 2007)	62,190	Iowa, Nth Carolina population, USA	171	SMR rSMR	0.81 (0.70, 0.95)* 1.53 (1.31, 1.78)*	- rationale and usefulness of rSMR as a measure
Dodge et al 2007	USA Agricultural workers	Retrospective cohort study	Ratios (among Californian Hispanic United Farm Union Members (working age), relative to other California Hispanics (1988-2001).	not reported	Californian Hispanic cancer registrants	256	HR ^c	0.75 (0.51, 1.11)	- denominator UFW data not reported
Abusaa et al 2004	USA Farmers, Agricultural workers	Retrospective cohort study	Ratios for Mississippi farmers aged 20-79 yrs (1995-1999) by race and region.	not reported	Mississippi all occupations, USA	102	PMR	2.43 (1.98, 2.92)*	- testicular & penile cancers included in ICD grouping - no separation of farmers vs. agricultural workers - unknown population denominator - some results table / text mismatches - speculative discussion on associations with secondary ecological data (not in results)
Fleming et al 2003	USA	Retrospective cohort / nested	Cox regression mortality analyses adjusted for survey	7746 199: 1122	Non-farmer National Health	571	RR	1.3 (0.8, 2.2)	- limited discussion on the prostate cancer findings

Five of the ten mortality studies reported increased prostate cancer mortality in farmers;⁵⁹⁻⁶³ four reported decreased mortality;^{33, 64-66} and one reported both an increase and decrease within the same cohort, using alternative outcome measures.⁵⁸ The proportion of studies with significant results tended to vary by region and outcome measures used.

Only one of the four European studies reported increased mortality in farmers with 95% confidence limits above unity.⁶³ The other three reported lower mortality ratios in farmers that were not statistically significant.⁶⁴⁻⁶⁶ In contrast, four of the six non-European studies reported increased mortality in farmers, two having lower 95% confidence limits above unity.⁵⁹⁻⁶⁰ One study had significant increases for some subgroups of farmers but not others, whilst results of the other study were not statistically significant.⁶¹⁻⁶² Only one non-European study reported a decrease in farmer mortality, but this was not statistically significant. The remaining study had internally inconsistent findings, with both significantly increased and decreased prostate cancer mortality for the same farmer cohort.⁵⁸

Studies that used PMR presented a different picture to those that made direct mortality rate comparisons. All three studies comparing PMR, reported statistically significant increases in farmer mortality.^{60-61,63} In contrast, only one of the four studies that used SMR (alone), reported a statistically significant increase.⁵⁹ The study with inconsistent internal findings, reported a significantly decreased SMR for prostate cancer in farmers, yet a significantly increased 'relative SMR' for the same cohort.⁵⁸

- *Incidence*

Five of nine incidence studies (Table 2.8) reported increased prostate cancer incidence in farmers compared to non-farmers;^{64, 67-70} but only two of these were statistically significant, both

from North America.⁶⁹⁻⁷⁰ None of the four studies reporting decreased incidence in farmers were statistically significant.⁷¹⁻⁷⁴

Table 2.8: Published studies reporting on differences in prostate cancer incidence between farmers and non-farmer groups (Jan 2002- Dec 2013)

Primary author, year, title of study	Country / Occupational sub-group	Study design	What was done	Total farmers in cohort (+/- cases : controls)	Non-farmer comparison group (age-matched)	No. farmer incident cases (+/- sub-groups)	Outcome measure	Rate ratio 95% CI	Limitations
European studies									
Frost et al 2011	United Kingdom Agricultural workers, Pesticide applicators ¹	Retrospective cohort study	Rates for agricultural pesticide users (1987-2004)	62,960	UK population	205	SIR	1.07 (0.93, 1.22)	- possible PSA test/access bias - unclear if study group includes farmers per se.
Pukkala et al 2009	Denmark, Finland, Iceland, Norway and Sweden Farmers, Agricultural workers	Retrospective cohort study	Rates by occupation for 5 Nordic countries for men aged 30-64 yrs (1961 to 2005),	not reported	National populations of 5 Nordic countries	41,025	SIR	0.99 (0.98, 1.00)	- possible PSA test access bias - no separation of farmers vs. agricultural workers - age limit 64 yrs
Laakkonen et al 2008	Finland Farmers, Agricultural workers	Retrospective cohort study	Rates of Finnish farmers, by type of farm (1995-2005)	33,025	FIN population	1,309	SIR	0.98 (0.93, 1.03)	- possible PSA test access bias - no separation of farmers vs. agricultural workers
Rafnsson et al 2006	Iceland Sheep farmers	Retrospective cohort study	Rates in a compulsory sheep-dipping registry (1962-2003) compared with the general population of Iceland	7,882	ICE population	541	SIR	0.92 (0.85, 1.00)	- possible PSA test access bias - results comparable to other lindane-dipping sheep farmers only
Zeegers et al 2004	Netherlands Farmers, Agricultural workers	Prospective cohort / nested case-control study	Total of 58,279 men (55-69 yrs) completed a questionnaire in 1986 on cancer risk factors & job history. Cancer incidence was	765	Netherlands population-based study sub-cohort.	Ever farmer n=54 Baseline	RR	0.86 (0.53, 1.14) 0.75 (0.39, 1.46)	- possible PSA test access bias - unclear if cohort are self-employed farmers, agricultural workers or both.

			followed to 1993. Cases were compared with sub-cohort controls for multivariate adjusted cancer incidence			farmer n=27 Longest job farmer n=27		0.70 (0.36,,1.36)	- relatively short follow-up; small number incident cases per job title; and wide confidence intervals
Settimi et al 2003	Italy Farmers, Agricultural workers	Case control study	A hospital-based multi-site case-control study was carried out in 5 rural areas (1990-92). Prostate cancer cases and 'other cancer' controls 20-75yrs of age were interviewed.	343 124:659	Rural hospital cancer controls	64	OR ^b	1.40 (0.9, 2.0)	- possible PSA test access bias - no separation of farmers vs. agricultural workers - relatively small number of incident cases - risk component of study analysed at 'ecological' level
Bouchardy et al 2002	Switzerland Farmers, Agricultural workers	Retrospective cohort / case-referent study	Case referent study, as no occupational denominator data available. Other cancer registrants were case referents. Cancer cases were 25-65 yrs in 5 Swiss states from (1980 -1993). Odds ratios for cancer type by occupation were estimated in reference to all other occupations, using logistic regression. Results were + /- a socio-economic (SES) indicator.	1,393 485: 8,641	Other cancer registry referents from other occupations	Agriculture & animal producers (all): n=485 • Adj. age, registry, urbanity, nationality • Add. adj. SES group Farmers & animal producers (only): n=310 • Adj. age, registry, urbanity, nationality • Add. adj. SES group	OR ^a	1.2 (0.9, 1.2) 1.2 (1.0, 1.2) 1.2 (1.0, 1.3) 1.2 (1.0, 1.4) (p<.05)*	- possible PSA test access bias - no separation of farmers vs. agricultural workers - age data limits (< 65yrs) required exclusion of 8.5% of cases, with implications for prostate cancer of 'older persons'. - high proportion of unclassified occupations

North American studies									
Koutros et al 2010	USA	Prospective cohort study	Rates amongst farmers / pesticide applicators (1993 to 2006)	52,394	Iowa & North Carolina populations	Iowa n=979 NC n=740 All n=1,719	SIR	1.22 (1.15, 1.30)* 1.16 (1.08, 1.24)* 1.19 (1.14, 1.25)*	- possible PSA test access bias
An update of cancer incidence in the agricultural health study	Farmers, Pesticide applicators ²								
Meyer et al 2007	USA	Case control study	Farming-related activities were analysed for prostate cancer cases and controls (65-79yrs) matched for age, race and region in South Carolina, USA (1999-2001). Adj.odds ratios (aOR) were estimated using by logistic regression.	411 405:392	South Carolina population controls.	Caucasian n=117 African-American n=107 All n=224	OR ^a	1.8 (1.3, 2.7)* 1.0 (0.6, 1.6) 1.40 (1.10, 1.90)*	- possible PSA test access bias - selection bias: response fair & less able to locate African-Americans - recall bias may favour cases over controls - no separation of farmers vs. agricultural workers
A case-control study of farming and prostate cancer in African-American and Caucasian men	Farmers, Agricultural workers								

Of the seven European studies, three found increased incidence;^{64, 67-68} and four found decreased incidence of prostate cancer in farmers.⁷¹⁻⁷⁴ None of these results were statistically significant, although results for two studies with decreased rates;^{71, 73} and one with increased rates in farmers,⁶⁸ were of borderline significance where the upper or lower 95% confidence limit (respectively), was equal to one.

2.6.5.5 Discussion

Whilst the findings were based on a comprehensive search and review of the available literature, only eighteen studies were eligible for inclusion. Over one third of mortality studies and nearly a quarter of incidence studies reviewed, reported statistically significant increases in prostate cancer risk in farmers compared to non-farmers. Similar to previous reviews there was considerable heterogeneity by geographic region, study design and degree of control for confounders.^{7, 15, 54} Likewise, a greater proportion of North American studies reported excesses in prostate cancer mortality than European studies; and more European studies used SMR outcome measures.

Given these inconsistencies and the small number of relevant studies retrieved, the volume and strength of the evidence for increased prostate cancer risk in farmers is weak or lacking; and probably less supportive of an excess of prostate cancer risk in farmers than previous reviews.^{7, 15, 54}

Geographical location and study design have been cited previously as important predictors for prostate cancer risk across studies, with a statistical interaction between these being reported.^{7, 15, 54} Increased risk was generally reported in studies that used PMR compared to SMR.⁵⁴

PMR tends to be used in studies that lack cohort or population denominator data. However, it is susceptible to over-estimating differences in mortality when a group has lower cancer mortality for all cancer and some common specific cancers (e.g. lung) such as has been reported for farmers.⁷⁵ Aquavella et al has suggested that an observed general reduction in the RR of prostate cancer in

farmers since the 1980's, could at least in part be due to the reduced influence of studies that use PMR within meta-analyses.⁷ This may partly explain the low level of evidence for increased prostate cancer mortality in farmers in this review, in which only three of the eighteen studies used PMR.

Alternatively, some have suggested that large cohort studies using SMR, are prone to 'mask' or under-estimate differences between groups, as they often lack information about confounding factors and are prone to the 'healthy worker effect'.⁷⁵ This effect is more likely for occupationally defined groups where overall cancer mortality is lower than that of the comparison population, which is the case for most studies of farmers. The opposing trends of PMR and SMR outcome measures have been noted in previous reviews and for prostate cancer mortality of farmers within the Agricultural Health Study cohort.⁵⁸

There were a range of limitations that have affected this study. Firstly, only English language articles were assessed, so that some publication bias is possible. There was also a general lack of detail around job title and occupational classifications. Studies used different occupational coding systems and/or national standards.⁷⁶⁻⁷⁹ Definitions of farmers and agricultural workers were often assumed rather than described in most articles, and selection of farmer cohorts was inconsistent across studies. Farmers and / or agricultural workers could be defined by 'occupation codes', by residential status, union membership or membership of pesticide registries; could be grouped together or assessed separately.

Studies also lacked detail on farming practice / exposures, which limits the ability to identify and control for potentially important confounders. Some confounders that were addressed through regression or cohort stratification were age, rural/regional differences;⁶⁸ socio-economic status (e.g. education, income, marital status);^{68, 71, 74} years in farming;^{70, 72} Caucasian vs. African American race;⁷⁰ lifestyle factors and family history of prostate cancer;⁷⁴ raising of animals;⁶⁸ and stage of diagnosis.³³ Smaller studies that controlled for such confounders however, sometimes had

insufficient power to detect weaker associations as statistically significant.^{67, 74} In contrast, larger population-wide studies may have had more precise confidence limits, but lacked detail on confounders.^{64, 71-72}

It is well known that prostate cancer more commonly presents in older age groups. However, despite the use of age-standardisation to control for age differences between groups within studies, the inclusion or exclusion of older age groups in a cohort, may affect comparison between studies. Inclusion of older age groups could mask a stronger association confined to younger age groups.⁵⁴ In addition, farmers often work well beyond conventional retirement age, but studies that differentiated groups by occupation codes, may not have included age-groups beyond traditional working age parameters, possibly rendering differences between farm and non-farm groups more difficult to detect.⁶⁸ If studies that use occupational coding and SMRs potentially under-estimate risk differences,⁵⁹ then any reported excess of prostate cancer in farmers using these parameters is particularly concerning, as they suggest an even higher risk in farmers is possible.

Exposure to pesticides was reported in a number of studies.^{67, 70, 73} These exposures are explored in a wider body of literature on cancer-pesticide associations that, in general, do not report on differences in incidence and mortality between farmers and non-farmers and are not within the scope of this review. However, the initial search did suggest that many more risk factor studies have been conducted over the past decade than incidence-mortality studies; and that most of these addressed pesticides. This may be in response to the previous research that had suggested a possible excess cancer risk in farmers; the large proportion of pesticide association studies originating from the Agricultural Health Study cohort;⁵⁶ and perhaps an extension of inquiry in the field, fuelled by recent progress in the understanding of biochemical and hormone-related carcinogenesis.

Future improvements in data linkage systems may also help address problems with lack of detail on some confounders. Inclusion and control for health service related variables (e.g. screening) may be possible. The impact of increased prostate specific antigen (PSA) testing on incidence rates has been identified broadly in population studies;⁸⁰ and may be relevant in the context of farmers.⁷¹⁻⁷² Whilst some studies suggest PSA testing may be less common among men living in rural areas,⁸¹⁻⁸² any studies specifically addressing PSA screening rates in farmers compared to non-farmers were not found. One study did report that farmers over 50yrs were less likely to have had a digital rectal examination of the prostate (an alternative screening technique).⁴¹ If it is subsequently found that farmers do have lower PSA screening rates, it would suggest a bias toward the null for any comparative incidence ratios not adjusted for this effect. The implication is that an excess of prostate cancer incidence might still exist in farmers of ‘very highly developed’ countries, but is being masked by differential PSA screening rates.

Future mortality studies, might also consider reporting both SMR and PMR measures, so the comparative impacts of ‘masking’ and ‘healthy worker’ bias upon risk estimates can be better assessed; and more valid comparisons with other studies made. Farmer cohorts need to be more carefully defined and differentiated beyond occupational coding. Similarly non-farmers of rural and urban origin must be better discerned. Although costs can be restrictive, large retrospective cohort studies need to be balanced by a greater number of more rigorously designed prospective studies, with improved detail on farm exposures and potential confounders. Regression analysis can then more systematically determine if any observed differences in prostate cancer risk might be attributable to specific farm exposures or characteristics of being a ‘farmer’.

2.6.5.6 Conclusion

This review found that around one third of mortality studies and one quarter of incidence studies reported significantly increased prostate cancer risk in farmers. There were a number of

study limitations and considerable heterogeneity by geographical region, design and outcome measures used, which affected the strength of evidence. Overall, the level of evidence for an excess of prostate cancer risk in farmers was weak. Future studies with more tightly controlled and consistent designs may provide further evidence regarding prostate cancer risk of farmers.

2.6.5.7 Acknowledgement

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Chapter 3: Methods

3.1 Study design

This cohort study was a mixed prospective and retrospective analysis of linked data. The 45 and Up Study cohort was the primary dataset of interest and formed the basis for comparisons of (a) farm residents; (b) non-farm rural residents; and (c) urban participants for a range of cancer and health-related variables. The sub-group of primary interest were those who stated they lived in a 'house on farm' in the 45 and up Study baseline questionnaire.

Cancers of interest for different components of the research were:

- Breast cancer
- Cervical cancer
- Colorectal cancer
- Lung cancer
- Melanoma
- Non Hodgkins Lymphoma
- Prostate cancer

There were two main components to the research. Firstly, there was a comparison of self-reported personal and behavioural risk factors of interest, as recorded on the 45 and Up Study baseline questionnaire. These were age, family history of cancer, household income, private insurance status, screening practices, diet, obesity, smoking and alcohol consumption. Secondly, a comparison of cancer mortality, incidence, stage at diagnoses, cancer screening practices and selected cancer treatments obtained via data linkage of participant records from the 45 and Up Study, with matching records from routine state and national health datasets.

3.1.1 The 45 and Up Study

The 45 and Up Study dataset has been made available to approved research projects from a range of institutions to conduct purpose-specific health research. The original concept was developed by a multi-institutional research collaboration, co-ordinated through the Sax Institute in New South Wales (NSW). A major partner is the Cancer Council NSW; and other partners include the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; NSW Government Family & Community Services – Ageing, Carers and the Disability Council NSW; the Australian Red Cross Blood Service; and the participants of the 45 and Up Study.¹⁻²

3.1.2 Sampling and recruitment

The sampling frame for the 45 and Up Study was the general population of the state of New South Wales, Australia. Those turning or aged 45 and over and resident in NSW were randomly sampled from the Australian Department of Human Services database (formerly Medicare Australia), which provides near complete coverage of the NSW population.²

Between January 2006 and December 2009, eligible individuals were invited to take part in the study via mail, which comprised of a letter of invitation, information leaflet, study questionnaire, consent form and a reply paid envelope. Participants joined the study by returning the completed questionnaire with signed consent form that allowed follow-up and linkage to routine health databases. Compared to urban and younger participants, individuals aged 80 years and over and residents of rural and remote areas, were oversampled by a ratio of 2:1. This was to ensure adequate numbers and representation of these smaller population groups.¹⁻²

The overall response rate for sampled individuals was approximately 17-18% allowing for mailing address errors. This rate is also variable across the different age/gender/location groups sampled. Individuals who had not been randomly sampled, but who met the eligibility criteria, could volunteer

to be part of the study by calling the study helpline. Approximately 0.5% of the final cohort volunteered to take part via this method.¹⁻²

The priority of the Study was to maximise heterogeneity of exposure, rather than representativeness; and whilst the response rate is comparable with other large cohort studies requiring consent for data linkage, it is not likely to be truly representative of the general population.

The complete sample size is subject to periodic revision and the version of the data project researchers received at the time of provisioning, but approximates 267,000. This represents approximately 11% of the NSW population aged 45 years and over in 2009.¹⁻²

3.2 Approval processes

Permission to access primary and secondary datasets was obtained from relevant data custodians, conditional upon meeting standard ethics principles for participant confidentiality and security of data. A range of scientific committee and ethics approvals were required prior to commencing the study. The original ethics approval obtained for the 45 and Up Study was granted by the University of New South Wales Human Research Ethics Committee (HREC). Separate participant consent was not required as part of this sub-study, because it was previously obtained as part of recruitment into the original 45 and Up Study cohort.

A preliminary approval for the sub-study was granted by the 45 and Up Study Scientific Advisory Committee, before submission of a full ethics application. Post-graduate research approval was also sought and granted from the University of Sydney Human Research Ethics Committee, which deferred authority to proceed according to conditions required by the NSW Population and Health Services Research Ethics Committee. Application for and approval for linkage of data was granted by the Centre for Health Record Linkage (CHeReL Ref: 2011.63). Final Ethics Committee Approval was granted for the project by the NSW Population and Health Services Research Ethics Committee

(PHSREC Ethics Approval Number 2012/07/408). As part of this approval, conditional support and/or sign-off was required of the following data custodians:

- Cancer Institute of NSW
- Department of Human Services (formerly Medicare Australia)
- NSW Ministry of Health
- NSW Pap Test Registry
- NSW Registry of Births, Deaths and Marriages
- The Sax Institute

3.3 Data access, linkage, security and preparation

3.3.1 Source datasets

The 45 and Up Study baseline survey formed the primary dataset of interest and provided:

- the primary means to identify, define and compare the three resident groups of interest
- self report data on a range of cancer related health variables
- records which could be further linked to secondary health datasets, to obtain further information on cancer indicators and other health service utilisation data over time.

Records of 45 and Up Study participants were identified within other routinely collected data in the:

- Australian Coordinating Registry (ACR) Cause of Death Unit Record File (COD URF)
- Medicare Benefits Schedule (MBS)
- NSW Admitted Patients Data Collection (APDC)
- NSW Cancer Registry (NSW CR)
- NSW Pap Test Register (PTR)
- NSW Register of Births, Deaths and Marriages (RBDM)

The Australian Coordinating Registry Cause of Death Unit Record File (COD URF) is a dataset jointly compiled by the NSW RBDM and the ABS (NSW). The RBDM registers all births and deaths in NSW. When a person is deceased, a Medical Certificate with Cause of Death is forwarded to the Registry, is recorded (uncoded) and a death registration number assigned. The RBDM then forwards the identifiable un-coded text information from the Medical Certificate Cause of Death, to the Australian Bureau of Statistics (ABS), which codes all the data. Cause of death is coded according to the International Statistical Classification of Diseases and Related Problems (ICD-9-CM or ICD-10-AM). Once the mortality data for a given year is complete and 'clean', the ABS removes personal identifiers (name and street address) to form the Australian Coordinating Registry COD URF.³⁻⁵ This information was used to analyse cancer-specific mortality of the cohort. In addition, the RBDM deaths registration data provided a means to validate deaths and death dates in other datasets, such as the APDC and NSW CR.

The MBS is part of the Medicare Benefits Scheme administered by the Australian Department of Human Services (formerly Medicare Australia); and is a record of all government funded health services itemised and subsidised by the Australian Government.⁶⁻⁷ This includes consultations for General Practitioners, diagnostic tests such as X-rays and pathology, plus most surgical and therapeutic procedures performed by registered medical or health professionals. The MBS data were used to assess visitations to General Practitioners and cancer screening procedures.

The APDC includes records for all hospital separations from every NSW public and private hospital plus day procedure centres.³⁻⁴ Records include a range of demographic data and administrative items, as well as other information such as cancer stage at diagnoses and procedures performed. The APDC data were used for comparison of hospitalisation for selected cancer therapies.

The NSW Cancer Registry maintains records of all cases of cancer diagnosed in NSW residents. Records include demographic data, staging information, year of diagnosis, and other coded information such as reason for death and morphology.^{3-4, 8} The NSW CR data were used to identify persons who developed cancer and corresponding cancer stage at diagnosis.

The Pap Test Register collects data on women who have a pap test in NSW and contains details of the woman undergoing the test and results of Pap tests, cervical histology tests or HPV DNA tests.^{3-4, 9} The PTR data were used to assess variations in cervical screening behaviours of the three cohorts.

3.3.2 Data linkage

Linkage of records for participants across datasets was both retrospective and prospective, depending on the date of recruitment of the participant into the 45 and Up Study; and the years of data covered in linked datasets. Names and selected demographic information from participants of the 45 and Up Study are combined into a file for matching with Master Linkage Key (MLK) records from other datasets.⁴

Linkage of the 45 and Up cohort data to the MBS data is done by the Sax Institute using a unique identifier provided to the Department of Human Services, which then released de-identified data to this study, as an approved project.^{1, 10} Linkage to records within datasets under NSW state jurisdiction was conducted by the NSW Centre for Health Record Linkage (CHeReL). A description of these methods follows, for which details are also available on the CHeReL website.¹¹

3.3.3 Master Linkage Key

To maintain participant confidentiality and privacy, health information is separated from personal identifying information, but has the potential to be linked between datasets through use of a Master Linkage Key (MLK). The MLK is continuously updated by the CheReL and available for 22

major NSW and ACT health datasets held by data custodians who have service agreements with the CHeReL to provide the service. The MLK process ensures that CHeReL staff performing the linkage use demographic variables but do not have access to clinical information about individuals. Data custodians only have access to data within their data collections. Researchers receive data which contains no identifying variables, or variables which provide a link back to the CHeReL MLK.¹¹⁻¹²

The Master Linkage Key uses identifying information in datasets, such as name, address, date of birth and gender (no health data), to generate a unique personal identifier or code number, that enables the identification of records for the same person located in each dataset (i.e. the 45 and Up Study, APDC, NSW CR, PTR and RBDM death registrations). This information is provided by data custodians to the CHeReL to construct the MLK on an ongoing basis. No health data is transferred in this process.¹¹⁻¹²

Records within the datasets were linked using probabilistic record linkage methods and ChoiceMaker software.¹³ ChoiceMaker uses 'blocking' and 'scoring' to identify definite and possible matches. During blocking, ChoiceMaker searches the target datasets for records which are possible matches to each other. There are two types of blocking. The exact blocking algorithm requires records to have the same set of valid fields and the same values for these fields. The automated blocking algorithm builds a set of conditions that are used to find as many records as possible that potentially match each other. Scoring employs a combination of a probabilistic decision, which is computed using a machine learning technique and absolute rules. This includes upper and lower probability cut-offs to determine the final decision as to whether each potential match denotes or possibly denotes the same person. Upper and lower probability cut-offs initially start at 0.75 and 0.25 for a linkage and are adjusted for each individual linkage to ensure false links are kept to a minimum. Record groups with probabilities in between the cut-offs are subject to clerical review.¹¹⁻¹³

The RBDM death records in the MLK extract were deterministically linked to COD URF records. This linkage was carried out using a five-step procedure:^{4, 13}

First pass	year of registration, encrypted registration number and exact date of death.
Second pass	year of registration, encrypted registration number and either: 1 day difference in date of death or same year of death or date of birth.
Third pass	year of registration, date of death, sex, postcode and date of birth.
Fourth pass	year of registration, date of death, sex, date of birth.
Fifth pass	date of death, sex and date of birth.

Initial data extractions for this study used MLK Version 2013_02 (45 and Up Study, APDC) and updated extractions MLK Version 2013_11 (NSW CR) and MLK Version 2015_13 (RBDM deaths and COD URF). Once linkages were finalised, the CHeReL created Project Person Numbers (PPN) for each person identified in the linkage and assigned PPNs to all 45 and Up Study, APDC, NSW CR, RBDM Death and PTR records. The CHeReL returned the PPN and the encrypted record number from the source databases to the data custodian. The data custodians supply datasets comprising the approved information from the source database plus the PPN to study researchers, who merged the datasets using the PPN for the purposes of the research project.⁴

3.3.4 Data linkage errors

Data obtained for administrative purposes, are known to be subject to human error regarding data entry (e.g. spelling, typographic). These can result in data linkage errors. The MLK is regularly checked for false positive linkages, with a false positive rate = 3/1,000 CHeReL PPN identifications (0.3%).⁴ For this study comprising of 267,119 persons from the 45 and Up Study, this converts to

linkage errors for approximately 800 persons. Detailed information about processes to minimise linkage errors is available from the CHeReL website.¹¹

3.3.5 Data provision, access and ongoing security

This study received data relating to 267,119 participants of the original 45 and Up Study cohort. Initial data were received in May 2013, with provision of updates from some databases received in October 2013 (NSW CR) and in December 2015 (RBDM and COD URF).⁴ A summary of records returned to Study Investigators appears in Table 3.1.

Table 3.1: Records returned to study investigators from data custodians

Measure	Record type	Number
45 and Up Study records	All 45 and Up records	267,119 records (267,119 persons)
MBS records	MBS records 6 Jan 2004 - 31 Dec 2011	46,012,797 records (265,532 persons)
APDC records	APDC records that linked to the 45 and Up records Separation date: 1 Feb 2006 - 30 Jun 2012	984,548 records (189,276 persons)
NSW CR records (Updated Oct 2013)	NSW CR records that linked to the 45 and Up records Notification date: 1 Feb 2006 - 31 Dec 2009	13,445 records (12,997 persons)
PTR records	PTR records that linked to 45 and Up records Test years: 2 Jan 2006 - 7 Mar 2013	234,673 records (78,510 persons)
RBDM Death records (Updated 2015)	RBDM Death records that linked to the 45 and Up records Death date: 1 Feb 2006 - 30 Jun 2013	16,692 records (16,602 persons)
COD URF (Updated 2015)	COD URF records that linked to RBDM death records* Death date: 1 Jan 2006 - 31 Dec 2013	16,603 records (16,592 persons)
Total Project Person Numbers (PPN)		(267,119 persons)

Encrypted and password protected data files were uploaded via a curated gateway to the Secure Unified Research Environment (SURE). The SURE is a secure computing environment operated through the Sax Institute, where project researchers log in to a research space remotely via an encrypted internet connection from a local computer. Researchers access and analyse data files provided by the data custodians within the SURE, thereby meeting the strict privacy and confidentiality conditions of ethics approvals and the terms of the SURE user agreement. All files moving into and out of the workspace were reviewed by the SURE curator to ensure no identifying information is transferred in or out of the workspace.¹⁴

3.4 Data scope and management of inconsistencies

Deaths and hospitalisations that occur outside of NSW for NSW residents are not captured / included in NSW datasets linked by the CHeReL.⁴ There are also some inconsistencies inherent in the

data due to software recognition transcription or data operator errors and whether PPN linkage was correct or not (e.g. dates of birth, death etc.).

3.4.1 Data custodian logic checks, missing data

The Sax Institute conducted some routine data checking on 45 and Up Study before data provision to systematically flag or minimise some errors where these did not interfere with data integrity. The following logic checks were undertaken by data custodians and data was recoded where appropriate.¹⁵

- If a participant entered a text response in a numerically coded field that could not be translated and numerically re-coded, values of invalid (99999) were applied.
- For age response questions, an automatic logic check was applied against the age at recruitment. For example, if the age entered on a response about a past event was greater than recruitment age, the response was coded invalid (99999).
- In questions which require a numeric response, if participants entered a range (e.g. 3-4). An average has been calculated in these instances, to produce a fraction.
- Range checks have been applied on certain numeric fields with truncation at upper and lower limits, to improve manageability and minimise data loss.
- For all female records, male-specific variables were left missing (rather than 0 or invalid) and vice versa.

Missing values in the 45 and Up Study data were indicated by a blank () when a participant failed to put a cross or number in a box when they should have. Conversely, invalid values were entered by electronic or manual data transcribers, when participants wrote in an implausible value for the response in question. For example, invalid values that failed range checks were coded 99999 for numeric response fields and X for alphanumeric fields. Details on invalid ranges applied in these range checks for each variable can be found in the 45 and Up Study Data Dictionary.^{11, 16}

Some correction of invalid values was possible because it is known from targeted checks on data quality that a sizeable proportion of them are due to operator error. This checking has entailed selection of invalid values and consulting scanned copies of questionnaires in which they occurred. In the sample checked, the invalid values were equally distributed between transcription errors and out-of-range responses given by participants themselves.¹⁵⁻¹⁶

The NSW Cancer Registry and Pap Test Register also conduct routine data quality control measures before release of data.⁸⁻⁹ These include monitoring notification or transmission rates by notifying General Practitioner or pathology laboratory, to ensure mandatory notification and reporting activity is maintained. Data entry validation checks and cross checks of data items, identity verification with the NSW Electoral Roll (by Pap test registry), periodic checks of coding accuracy and reliability, reconciliation of information from multiple sources, examination of multiple registrations, collaboration with pathologists, test providers, medical experts and other cancer registries and use of international coding and program conventions.^{3, 8-9, 17}

3.4.2 Other checks and data cleaning by researchers

As well as general logic checks performed by data custodians, we conducted routine data and logic checks throughout the analysis - especially after merging of datasets. Similar to most research projects using 45 and Up Study data, this study has excluded records with missing or invalid values for important variables from analyses, whilst reporting the total number of records available for each analysis. Due to the size of the dataset, this approach has generally not had a material impact on the statistical precision of the results of the analysis in other studies based on the 45 and Up Study data.³ However, where the creation of subsets of data has resulted in smaller baseline samples available for analyses compared to all possible records, the potential for bias has been noted in the results, such as when missing cases represented more than 10% of the available sample for any particular analyses. This is consistent with the approach taken in other studies on this cohort.¹⁸

Data sorting and summary statistics were run in SAS 9.3™ software for numeric variables, plausibility of dates across datasets checked; and frequency tables run for categorical variables to help identify duplicate records; missing data; large numbers, illogical combinations of demographic and clinical variables (e.g. male pap smears) and other unlikely combinations. Duplicate data were identified for further scrutiny or removal.

Inconsistent records across datasets may have resulted from transcription errors at data entry level or were false positives in the data linkage process. For example, if a person had a death date before hospital admission date, this may have been a date entry error in either dataset or a linkage of records from two different people. The latter can occur because the CHeReL carries out linkage using demographic variables and does not have access to the clinical component of records to conduct logic checks using clinical information.⁴ In some instances, cross-checking with a third dataset could resolve inconsistencies (e.g. where death date could be confirmed elsewhere); but where uncertainty remained as to which type of error had occurred after cross-checking, such records were removed from analyses.

3.5 Definition and description of key variables

Description of variables used in this study including wording of questions and response coding, is available in the various data dictionaries provided by data custodians for different datasets.

- 45 and Up Study Data dictionary^{3, 15}
- ABS mortality data - variable information^{3, 5}
- APDC Admitted Patient Data - variable information^{3, 19}
- NSW Cancer Registry Data Dictionary^{3, 8, 17}
- NSW RBDM death registrations - variable information^{3, 5}
- The Sax MBS Data dictionary⁶

Other documents with a description of items and variables include the 45 and Up Study baseline questionnaire databooks and the MBS Schedule.^{7, 20}

3.5.1 Accessibility/Remoteness Index of Australia (ARIA+) and 'distance to health service'

Two purpose-specific variables required for this study were supplied by the data custodians via the ChereL. These were the Accessibility/Remoteness Index of Australia (ARIA+); and the 'distance to health service' data. The method for calculating distances from non-disclosed residential addresses to nearest hospital was as follows:

"The CHereL calculated distances by obtaining latitude and longitude co-ordinates (geocodes) for hospitals and residential addresses for APDC records from the Ministry of Health. The geodesic distance between the residential address and hospital was calculated for each record where this information was available, using the Transact SQL 'STDistance' function, which gives a close approximation of the geodesic (great circle) distance between two points on the earth's surface. For 1,103 records, no distances could be calculated." ⁴

ARIA+ is a Australian Statistical Geography Standard (ASGS) endorsed measure of remoteness, derived from road distances between populated localities and Service Centres.²¹⁻²² An ARIA+ score for each participant was required to differentiate between rural and urban residents. These scores enabled each participant to be assigned to one of the following ASGS 'Remoteness Area' categories:

- Major City
- Inner Regional
- Outer Regional
- Remote
- Very Remote

3.5.2 Derivation of the 'cohort' variable

Sub-groups were defined for the 267,119 participant records of the '45 & Up Study' supplied to study researchers in May 2013. Two questionnaire variables were used to derive the new 'cohort' variable. These were:

1. Restricted Variable Name: ARIA plus_mean

Variable label: Accessibility/Remoteness Index of Australia (2006) ARIA+ mean (derived from postcode at recruitment)

2. Variable name: Current housing

Variable label: What best describes your current housing?

Question number: 14 (version 1) or 15 (version 2)

SAS format label: 3 = House on Farm (of 8 options)

'Farm residents' were defined as those who indicated that they live in a 'house on farm' on the 45 and Up Study baseline questionnaire. Rural 'non-farm' and urban residents were further defined by ARIA+/ ASGS category. Those participants who did not live in a house on a farm whose ARIA+/ ASGS classification indicated they did not live in a 'Major city', were defined as rural non-farm residents. The remaining group, defined as 'urban residents', were those who specified that they lived in a major city.

There were 194 participant records for which an ARIA+ score was not available to determine their ASGS classification. In this case, residential postcodes and /or the location and distance to any treating hospitals of linked APDC records were checked to determine allocation to residential sub-group. Frequency tables and logic checks were then conducted on all records to ensure no participants were missing or misclassified by the resident group derivation.

3.6 Limitations of datasets

3.6.1 Validity, representativeness and generalisability

It was important that the cohort as a whole and each resident sub-group, adequately represented their respective groups in the population. As only internal comparisons were conducted, this was less for reasons of generalisability than for preservation of the characteristics and exposures that differentiate or define farm residents from other rural and urban people. This is essential to the objectives and internal validity of the research in comparing groups; the latter enhanced by efforts to minimise random variation, systematic bias and confounding. However, representativeness of the cohort and its sub-groups, may enable some generalisations to be made regarding possible differences in the wider population under certain conditions.

In the first instance, representativeness of the 45 and Up cohort as a whole should be considered. A statement on limitations regarding the 45 and Up data, has been released from the Sax Institute:

“Because of the nature of cohort studies, including the “healthy cohort effect”, the 45 and Up Study will not necessarily be representative of the general NSW population 45 and over, nor is it designed to be. Research projects using the Study relate to internal comparisons within the cohort, which, provided sufficient heterogeneity of exposure is present, are valid and underlie the many contributions that cohort studies have made to the understanding of health world-wide, despite being derived from specific population sub-groups..... The 45 and Up Study is likely to be among the most representative large-scale cohort studies conducted world-wide.”²⁰

For associations between 45 and Up Study variables, or between one 45 and Up Study variable and a data item from a linked dataset, however, a higher level of generalisability has been reported; with results directly comparable with results of other studies of the same population.^{16, 23}

The 45 and Up Study questionnaire was only available in English, limiting participation of people with insufficient literacy in English. However, the study population is still relatively heterogeneous, with a good spread of responses across most variables. Importantly for this study, the oversampling of people from rural areas and 80 years and over (with no upper age limit), has enabled an adequate number of these sub-groups for internal comparisons within the cohort.¹ The 45 and Up Study cohort constitutes approximately one in ten NSW residents aged 45 years and over.²⁰ This is likely to be a higher ratio for the farm and rural non-farm cohorts, due to the oversampling of rural areas. This may affect the proportions of rural to urban people in the cohort compared to the wider population, but as comparisons are internal, this is not a particular issue.

More importantly, the definition of a farm resident was open to interpretation by participants completing the 45 and Up Study baseline questionnaire, with subsequent allocation to each sub-group depended upon this and ARIA+ index. This may well affect both the representativeness of sub-groups and internal validity of comparisons made, contributing to a bias toward the null for some analyses. It is also not known what proportion of those who stated they lived on a 'house on farm' live on commercial farms compared to lifestyle farms or acreage. Demographic and lifestyle characteristics and environmental exposures may vary for those living on a farm, depending upon whether work or leisure activities dominate. Differences in health related factors between farm and rural non-farm residents may only be small, due to this mix in the characteristics of those who live on-farm.

3.6.2 Cancer incident data limitations

The NSW CR advised that due to delays in receiving mortality data from the ABS, under-reporting of cancer incident cases for 2009 of approximately 1.7% for all cancers is expected. This is because a proportion of cancer cases are only identified and coded as new cases, on receipt of Australian Bureau of Statistics (ABS) death data. These are known as 'Death Certificate Only' (DCO)

cases, which were not registered as cancer cases at the time of diagnosis. Under-reporting rates for specific cancers analysed in this study by age group, are outlined in Table 3.2.²⁴ Notwithstanding this limitation, it is unlikely to impact this analysis to any great degree, as the focus was a comparison between cohorts, with under-reporting not likely to impact one group more than another.

Table 3.2: Proportion of NSW 'death certificate only' cancer cases, 2004- 2008 by tumour and age

Code	Tumor Group	%DCO*	5 Year Agegrp	DCO%
C910	Acute lymphoblastic leukaemia	0.4%	45-49 years	0.2%
C920	Acute myeloid leukaemia	1.8%	50-54 years	0.3%
C71	Brain	1.6%	55-59 years	0.2%
C50	Breast	0.7%	60-64 years	0.3%
C72	Central nervous system	1.4%	65-69 years	0.6%
C53	Cervix	1.0%	70-74 years	1.0%
C18	Colon	1.4%	75-79 years	1.7%
C69	Eye	0.4%	80-84 years	3.5%
C334	Lung	3.2%		
C43	Melanoma of skin	0.2%		
C8890	Multiple myeloma	3.1%		
C82	Non-Hodgkin's lymphoma	1.0%		
C919	Other lymphoid leukaemias	4.5%		
C929	Other myeloid leukaemia	3.0%		
C61	Prostate	0.9%		
C1921	Rectum, rectosigmoid, anus	0.6%		

3.7 Analysis

The following section provides an overall description of analysis methods. Further details are provided in following chapters, relating to specific components of the study.

3.7.1 Characteristics of farm, rural non-farm and urban residents in the 45 and Up Study cohort

Summary characteristics of the cohort by sub-group and gender were summarised for a range of health-related, behavioural and socio-economic variables. Descriptive and basic analytical statistics were generated in SAS 9.3™ using the PROC FREQ, PROC MEANS, PROC UNIVARIATE, PROC ANOVA

functions; and CHISQ and TEST and CL options. Cohort variables of particular interest compared and used in further analyses were:

- Age and sex
- Body Mass Index: categorical variable derived for 'overweight or obese' status
- Smoking: categorical variable derived for 'current, past or never smoker' status
- Alcohol consumption: categorical variables derived reflecting 'at risk' alcohol consumption guidelines. These were 'number of drinks per week' - used to derive a variable defined as risk consumption of more than 2 alcohol drinks per day; and 'number of days per week' - used to derive a variable defined as risk consumption of less than 2 alcohol free days per week.²⁵
- Annual household income: in the absence of the access-restricted SEIFA variable, a binary income indicator defined by an annual household income of \$70,000 or more approximated the 2006 average household income in NSW.²⁶
- Self reported screening / and years ago: status and categorical frequency variables derived for prostate, breast and bowel cancers reflecting recommended screening frequency guidelines (i.e. every 2 years).²⁷⁻²⁹
- Self reported cancer : for exclusion purposes
- First degree relative (mother, father, brother/sister) with selected cancers - to derive 'family history' risk factor variable for breast, bowel, prostate cancers and melanoma
- Red meat consumption: variable derived reflecting recommended dietary guidelines³⁰
- Sun exposure weekdays: variable derived for working week sun exposure reflecting recreational versus occupational patterns and exposure risk³¹
- Private health insurance with extras status
- Tannability: related to melanoma risk factors

Self reported incidence of cancer was not be used to validate NSW CR incident data, as the former was effectively a measure of prevalence within the cohort (presence of cancer prior to survey completion). Diagnosis of self reported cancer may have occurred well before recruitment into the study (pre 2005-2009). In addition, self reported existence (prevalence) of cancer was only valid for the point in time or 'year' in which the survey was conducted, whereas NSW CR data extended from the time of recruitment until 2009, attrition or death.

3.7.2 Cancer incidence and mortality rates and ratios

Cause of death data from January 2006 to December 2012 was checked against RBDM data for verification of death dates and removal of duplicate records. The mortality dataset was then merged with the 45 and Up Study dataset and further logic and date checks conducted. For each selected cancer, person-years for each participant over the period were calculated from the date of recruitment to date of death or censorship date of 31st December 2012. The 'Lexis macro' was used within SAS 9.3TM to split person-years for each participant across 5-year age-bands at risk, commencing from age at recruitment.³²⁻³³ This enabled correct allocation of risk time to each age strata, as the person aged. Thirty three records for which recruitment dates were found to be incorrect were removed, as person-years could not be calculated.

Similar methods were employed for preparation of data to calculate cancer incidence rates and ratios. In this case, 45 and Up Study data were merged with NSW CR data for the 2006-2009 period. For selected cancers, person-years were calculated commencing from 1st February 2006 to censorship or the 14th day of the month of diagnosis, since the actual date of diagnosis was not provided. Separate analyses on cancer-specific subsets of data, with different person-year calculations for each cancer type, enabled persons who were registered with the NSW CR with more than one type of cancer to be accommodated. Cancer codes used to identify particular cancers for

incidence and mortality ratios were as listed in relevant data dictionaries;³ and consistent with ICD10-AM listings.³⁴

For each cancer and gender, frequencies of observed incident and mortality events were determined using SAS 9.3TM. Person-years for different age-at-risk strata were also generated and both values used to create age-standardisation tables. Direct and indirect age-standardisation methods were used to calculate incidence and mortality rates and ratios for each gender and each sub-cohort for the selected cancers, according to methods described by Taylor et al.³⁵ Variance of observed counts were calculated based on the Poisson distribution, where there were fewer than 30 observed cases or events.³⁵ Incidence and mortality rates and ratios were generated for prostate, breast, colorectal, lung, melanoma, non-Hodgkins Lymphoma (NHL), multiple myeloma, myeloid leukaemia, lymphocytic leukaemia and eye/brain/central nervous system cancers and cervical cancers. However, only the first six cancers were reported upon, due to low case numbers of the less common cancers in the farm group.

In this study the reference population used for comparison of age-standardised incident and mortality rates and ratios was the whole 45 and Up Study cohort, to ensure valid internal comparisons as described previously.^{1, 20} For indirect age-standardisation, the age-specific rates of the standard population (45 and Up Study cohort) are applied to the age structure of the subject population (resident sub-group) to give an expected number of events. The observed number of events is then compared to that expected and expressed as an incidence or mortality ratio (observed/expected). Compared to direct age-standardisation, the variance is minimised and confidence intervals are narrower, helpful for determining statistical significance for smaller populations.³⁵

Direct age-standardisation methods apply the age-specific structure of sub-groups to the age structure of the standard population, to give an overall rate that would have occurred in the subject

population if it had the standard age-profile. This is only possible in datasets where observed events were known by age-group, which was the case in our study. Direct age-standardisation is the preferred method for comparing sub-groups against each other; and for comparisons over time. A disadvantage of this method is that calculated rates can become unstable with a small number of events.³⁵ Results using both methods were compared, but direct age-standardisation rates and ratios were deemed the most appropriate and are reported in this thesis.

3.7.3 Cancer incidence and mortality hazard ratios

Cox Proportional Hazards regression was used to determine potential differences in incidence or mortality by gender, between farm, rural non-farm and urban residents, controlling for other variables. The selected cancers modelled were the same as those for standardised mortality and incidence ratios, being prostate, breast, colorectal and lung cancer, melanoma and NHL.

Modelling was performed using log rank tests and proportional hazards regression in SAS 9.3™. Whilst not all variables were used in all models, the following variables were initially considered for inclusion:

- Cohort (farm, rural non-farm and urban residence) - the variable of primary interest
- Annual household income over \$70,000
- Overweight status - Body Mass Index>25
- Alcohol risk drinking status - drinks (risk>2+/day), days (risk> 5 /week)
- Smoking - ever, past, current
- Family history of cancer - prostate, breast, lung, colorectal cancer and melanoma
- Sun exposure category - (< 1 hour, 2-3 hours, 4hours+)
- Red meat consumption category - (<3 serves, 3-4 serves, 4+ serves/week)
- Tannability (melanoma only)

Variables with univariate $p < .25$ were included in the base model with appropriate dummy variables and interaction terms. Models were progressively assessed using backward elimination methods to the .05 level, with non-significant variables also checked for confounding effects on hazard ratios of cohort groups. Residual plots were examined to ensure that the assumptions of proportional hazards regression were met.

Analyses using Cox Regression and presented as adjusted hazard ratios in this study, were able to control for a range of factors. Thus the adjusted hazard ratios may be considered more informative than standardised incidence and mortality rate ratios as a measure of incidence and mortality risk in this study. However, SMR and SIR results are also included in the analysis to allow for (1) direct comparisons with other studies which have used these measures in the absence of risk factor information; (2) to gauge the effects of these additional risk factors compared to age alone; (3) to cross-check consistency of results when using different outcome measures.

3.7.4 Stage at diagnosis

The 'stage at diagnosis' variable was derived from 'degree of spread', as described in the NSW CR data dictionary.¹⁷ This binary categorical variable was defined by 'Stage 2 or above' status. Chi-squared analyses for more common cancers were conducted for both stage at diagnosis and screening frequency categories, against a range of other variables. Only prostate, breast and colorectal cancer cases were assessed for stage at diagnosis, due to the low number of less common cancers newly diagnosed within the cohort over the 2006-2009 period.

Logistic regression was used to model potential differences in stage at diagnosis between farm, rural non-farm and urban cohorts, controlling for other variables. Variables considered were those listed for incidence and mortality, plus a range of health, economic and behavioural risk factors. In addition, the effect of selected cancer screening was considered. Cases where stage was not recorded were excluded from analysis. Binary logistic regression was used to calculate adjusted odds

ratios for later stage cancer, controlling for selected risk factors. Variables with univariate p values < .25 were included in the base model, with all possible interaction terms. Models were progressively reduced using a backward elimination approach, removing non-significant variables (at the .05 level), accounting for any non-significant confounders. Residual plots were examined to identify cases with undue influence in regression models.

3.7.5 Cancer screening

Frequency of screening for breast, prostate, cervical and bowel cancers were compared using a range of datasets for parallel comparison. These consisted of the self reported frequency of screening in the 45 and Up Study (2006-2009); number of screening test items and General Practitioner visits claimed through the MBS (2004-2011); and the number of cervical screening tests in the NSW Pap Test Register (2006-2013). Binary logistic regression was used to model effects on self reported screening using similar methods as described for stage at diagnosis. The age-adjusted average number of screening tests and visits to General Practitioners over the specified periods were also compared using analysis of covariance.

3.7.6 Cancer treatments in the NSW Admitted Patients Data Collection

Data from the NSW APDC were used to compare surgical, chemotherapy, radiotherapy and brachytherapy procedures for those with a diagnosis of prostate, breast or colorectal cancer over the period. Average distance to treating hospital for each therapy was determined and binary logistic regression was used to compare the odds of receiving treatment by resident group for each cancer, controlling for selected variables. Criteria for inclusion, significance levels and elimination methods were as described for stage at diagnosis. Procedures assessed were excision of breast lesion, mastectomy, radical prostatectomy, radiotherapy, chemotherapy and brachytherapy, as defined within the APDC data dictionary.³

In conclusion, this Chapter has primarily focused on the methods used to prepare the data for analyses. Further details about the datasets and variables used in this study can be found on the appropriate websites and data dictionaries referenced throughout the chapter. The following chapters will reiterate these methods in part, as necessary to fulfill requirements for manuscripts submitted for publication. Further detail on analytical methods undertaken as they pertain to specific study components, is also provided.

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Chapter 4: Cancer risk factors and mortality in farm, rural non-farm and urban residents within the 45 and Up Study cohort

This chapter is a manuscript that was prepared for submission to a peer reviewed journal.

Depczynski J, Dobbins T, Armstrong B, Lower T. **Cancer risk factors and mortality in farm, rural non-farm and urban residents within the 45 and Up Study cohort.** Manuscript prepared for review.

4.1 Abstract

Introduction: People living in rural areas in Australia have poorer cancer outcomes than those in urban areas, but it is not known if this is the case for farm residents. **Methods:** Data for farm, rural non-farm and urban participants of the 45 and Up Study cohort in New South Wales, Australia, were linked with state death registrations data for 2006 - 2012. Direct age-standardised mortality ratios for 267,074 participants were compared for all cancer and prostate, breast, lung and colorectal cancers, non-Hodgkins Lymphoma (NHL) and melanoma. Proportional hazards regression was used to estimate adjusted mortality hazard ratios for each cancer type, controlling for common risk factors. **Results:** Farm, rural non-farm and urban residents differed in a range of health related characteristics. Farm women had a significantly lower adjusted hazard ratio for breast cancer than rural non-farm women. Confidence intervals for adjusted hazard of all cancer and other selected cancers did not exclude unity, but point estimates suggested farm residents had non-significantly lower all cancer and colorectal cancer mortality risk; similar lung cancer risk; and farm men slightly elevated melanoma and prostate cancer risk. **Conclusion:** Farm women had a significantly lower breast cancer mortality risk than rural non-farm women, but differences between farm, rural non-farm and urban residents for all cancer or other selected cancers were not significant.

Keywords: Farm* risk, mortality, cancer, prostate, breast, melanoma, lung, colorectal, NHL

4.2 Introduction

Cancers are responsible for approximately one third of all deaths in Australia, with lung, lympho-haematopoietic, colorectal, prostate and breast cancers responsible for most deaths.¹⁻² Rural Australians have higher mortality from all cancer, melanoma, lung, prostate and colorectal cancer than those who live in major cities.³ Cancer mortality statistics have been reported by rurality based on the Accessibility/Remoteness Index of Australia (ARIA+), but this does not identify farm residents as a sub-group.³⁻⁶ There is currently no information available on cancer mortality differences between farm, rural non-farm and urban residents in Australia.

There were around 43,500 farm businesses registered in the state of New South Wales (NSW) in 2010-2011⁷ and approximately 35,000 farmers and farm workers aged 45 years or over. Almost 90% of Australian farms in 2010-11 were family businesses run by owner-operators or contributing family workers.⁸ A previous Australian study of mortality in male farmers reported a significantly higher standardised mortality ratio (SMR) for prostate cancer; and non-significant elevations in other cancers, compared to the national population.⁹ International studies of cancer mortality in farmers have reported mixed findings.¹⁰⁻²³ Compared to earlier reports, more recent studies have tended to be less conclusive regarding excess cancer risk in farmers.^{9, 24-31} It is not known if this is due to an improved mortality profile or a general change in study measures and designs. Methodological problems include small sample sizes, lack of control for confounders and a range of locations and time periods, such that the number of comparative studies on which to form conclusions on any particular cancer is small.^{16, 32} As most studies have been occupationally based, this has also meant there is less information about cancers amongst women on farms, many of whom work unpaid on-farm as well as engage in off-farm work to support family incomes.³³

An analysis of comparative cancer mortality in farmers that addresses some of these issues is overdue for Australia. This study aimed to identify differences in cancer mortality from common cancers, between farm, non-farm rural and urban residents; controlling for selected risk factors previously associated with cancer mortality.

4.3 Methods

This data linkage study was based on the 45 and Up Study cohort, comprising 267,119 residents of NSW, Australia; and managed by the Sax Institute, in collaboration with major health agency partners.

4.3.1 Sampling and recruitment

Between January 2006 and December 2009, eligible NSW individuals 45 years and over, were randomly sampled from the Australian Department of Human Services database, which provides near complete coverage of the NSW population, Persons aged 80 years and over and residents of rural and remote areas were oversampled by a ratio of 2:1. Subjects were mailed a questionnaire with consent form for follow-up and data linkage to routine health databases. An additional 0.5% of the final cohort comprised volunteers who contacted the Study hotline to participate. The overall response rate for sampled individuals was 17-18%; representing approximately 11% of the NSW population aged 45 years and over.³⁴ Further information about the study cohort is available from the 45 and Up Study website.³⁵

4.3.2 Datasets, data linkage and checks

Participant records from the 45 and Up Study provided information on residence (farm, rural or urban), age, family history of cancer, household income, screening practices, diet, obesity, sun exposure, smoking and alcohol consumption. Cancer mortality for the three resident sub-groups was compared by data linkage with deaths registrations in the NSW Registry of Births, Deaths and

Marriages (RBDM); and the Cause of Death Unit Record File^a held by the NSW Ministry of Health's Secure Analytics for Population Health Research and Intelligence. Cause of death was coded according to the International Statistical Classification of Diseases and Related Problems Tenth Revision (ICD-10).³⁶ Data linkage was conducted by the NSW Centre for Health Record Linkage, using a probabilistic record linkage method.³⁷ Detailed information on data linkage methods is available elsewhere.³⁸

Routine data frequency and logic checks were undertaken to check for plausibility of dates and ranges, duplicate records, missing data, large numbers and illogical combinations of demographic, clinical variables and other unlikely combinations. Records with missing or invalid values for important variables of interest were excluded from analyses; and noted where these represented more than 10% of the available sample. Inconsistent data resulting from transcription errors or false positive linkages (e.g. death date before recruitment date), which could not be resolved by cross-checking were also removed from analysis. Description of survey questions, response coding and sample checking procedures can be found in the NSW Mortality and 45 and Up data dictionaries.³⁹⁻⁴⁰

4.3.3 Derivation of the 'cohort-defining' variable

'Farm residents' were defined as those who indicated that they lived in a 'house on farm' in the 45 and Up Study baseline questionnaire. Rural 'non-farm' and urban residents were further defined using ARIA+ classification, by postcode of residence at recruitment.^{3, 5} Those participants whose ARIA+ classification indicated they did not live in a 'Major city', excluding those who also specified that they lived in a 'house on farm', were defined as rural non-farm residents. The remaining 'urban' participants were those who lived in a 'Major city'. Cross-tabulation and logic checks were conducted on this derivation to ensure no participants were missing or misclassified. Where ARIA+

^a The Cause of Death Unit Record File (COD URF) is provided by the Australian Coordinating Registry for COD URF on behalf of Australian Registries of Births, Deaths and Marriages, Australian Coroners and the National Coronial Information System

was not recorded, allocation was determined by cross-checking postcode of residence in a linked hospital dataset.

4.3.4 Analytical procedures

Frequency and analytical procedures were conducted using in SAS 9.3™ analytical software and Microsoft Excel 2007.™⁴¹⁻⁴² Summary descriptive statistics by cohort and gender were generated for selected health and lifestyle risk factors. Where relevant, adjusted means were calculated using least squares methods. Some variables were re-classified to align with current national health or workplace recommendations; or those in place at the time of recruitment.⁴³⁻⁴⁸ These related to smoking status, risky alcohol consumption, overweight and obesity, red meat consumption and weekday sun exposure. Household income was categorised to approximate levels above or below the 2006 average household income in NSW in 2006.⁴⁹ Tannability, the response of participants' skin when repeatedly exposed to sunlight in summer without protection (never, mild, moderate, very), was considered for melanoma models only.

For each selected cancer, person-years for each participant were calculated from the date of recruitment to date of death or censorship at 31st December 2012. Person-years for each participant were split across 5-year age-bands at risk, commencing from age at recruitment, to enable allocation of risk time to each age stratum, as the person aged.⁵⁰⁻⁵¹ Observed mortality events and total person-years for each cancer were determined by gender, age-band-at-risk stratum and cohort. Direct age-standardisation methods were used to calculate mortality rates and ratios. Variances of observed counts were calculated based on the Normal approximation or the Poisson distribution where less than 30 observed events occurred.⁵² Consistent with 45 and Up Study Collaboration recommendations, only internal comparisons between sub-groups within the cohort were made, with the reference population being the whole 45 and Up Study cohort.³⁴ Direct age-standardised

mortality rates and ratios were generated for all cancers and the cancers of interest - prostate, breast, colorectal and lung, melanoma and non-Hodgkins Lymphoma (NHL).

Cox Proportional Hazards regression was used to model potential differences in mortality for selected cancers by cohort, controlling for risk factors.⁵³ Variables with univariate logrank p values < .25 were included in the base model. Interaction terms between variables of interest in the base model and cohort were created and tested for effect modification. Models were progressively assessed using backward elimination methods to the .05 level, with non-significant variables also checked for confounding effects on hazard ratios of cohort groups. Residual plots were examined to ensure that the assumptions of proportional hazards regression were met.

4.4 Results

Information from the 45 and Up Study survey questionnaire was available for 267,119 participants. Forty five participant records were removed for which dates of recruitment, age or gender information across datasets was incomplete or inconsistent. Analysis was undertaken for the remaining 267,074 participants, who were followed for 1,128,162 person-years (mean 4.2 years /person, max 7.4 years).

Summary characteristics of the cohort for each gender are shown in Table 1. Farm residents were notably younger than rural non-farm and urban residents. Averages for other quantitative variables were adjusted for age. Differences in smoking status, alcohol consumption, overweight/obesity, tannability and family history of selected cancers were generally small. In contrast, farm residents had noticeably higher average sun exposure and red meat consumption; and considerably more urban residents had annual household incomes over the median level.

Table 4.1: Selected characteristics of farm, rural non-farm and urban residents reported in the 45 and Up Study baseline questionnaire

Characteristics	Men				Women			
	Total	Farm	Rural	Urban	Total	Farm	Rural	Urban
	n	% or mean (95 % CI)	% or mean (95 % CI)	% or mean (95 % CI)	n	% or mean (95 % CI)	% or mean (95 % CI)	% or mean (95 % CI)
Age at recruitment (years)								
45-49	10,698	10.2%	8.4%	8.6%	16,654	14.0%	11.4%	11.4%
50-54	17,630	16.2%	13.2%	14.9%	25,285	21.3%	16.9%	17.9%
55-59	19,748	18.4%	15.6%	15.9%	25,706	22.3%	17.3%	18.0%
60-64	19,206	18.9%	15.9%	14.6%	22,118	17.3%	16.0%	14.6%
65-69	17,340	15.6%	15.3%	12.4%	17,766	12.3%	13.9%	10.8%
70-74	13,480	9.8%	12.4%	9.5%	12,534	6.5%	9.9%	7.9%
75-79	10,192	5.9%	9.4%	7.4%	8,649	3.6%	6.8%	5.6%
80-84	10,983	3.8%	7.2%	11.4%	8,791	1.9%	4.8%	8.3%
85+	4,605	1.1%	2.7%	5.2%	5,689	0.7%	3.0%	5.6%
<i>Average age</i>	<i>123,882</i>	<i>61.2 (61.0 - 61.4)</i>	<i>63.7 (63.6 - 63.8)</i>	<i>64.3 (64.2 - 64.4)</i>	<i>143,192</i>	<i>58.6 (58.5 - 58.8)</i>	<i>61.8 (61.7 - 61.8)</i>	<i>62.5 (62.4 - 62.5)</i>
Smoking status (n)								
Never	54,963	48.2%	41.8%	46.4%	85,481	61.4%	57.9%	61.4%
Past	59,413	44.0%	50.1%	46.6%	47,774	32.1%	34.4%	32.5%
Current	9,444	7.8%	8.2%	7.1%	9,885	6.5%	7.7%	6.1%
Alcohol consumption - drinks								
> 2 drinks/day	28,904	24.4%	25.8%	21.5%	8,542	6.7%	6.2%	5.9%
<i>Av. drinks / week (age adjusted)</i>	<i>121,791</i>	<i>9.9 (9.7 - 10.1)</i>	<i>10.5 (10.4 - 10.6)</i>	<i>9.2 (9.1 - 9.3)</i>	<i>139,564</i>	<i>4.6 (4.5 - 4.7)</i>	<i>4.5 (4.4 - 4.5)</i>	<i>4.4 (4.4 - 4.5)</i>
Alcohol consumption - days								
> 5 days/week	39,036	36.7%	34.9%	31.6%	25,551	22.7%	20.2%	19.6%
<i>Av. days / week (age adjusted)</i>	<i>116,529</i>	<i>3.8 (3.8 - 3.9)</i>	<i>3.7 (3.7 - 3.7)</i>	<i>3.5 (3.5 - 3.5)</i>	<i>127,087^a</i>	<i>2.8 (2.8 - 2.9)</i>	<i>2.6 (2.6 - 2.6)</i>	<i>2.6 (2.6 - 2.6)</i>
Body Mass Index (BMI)								
BMI >25	79,310	69.4%	70.8%	65.8%	72,682	54.5%	58.5%	52.4%
<i>Av. BMI (age adjusted)</i>	<i>115,985</i>	<i>27.0 (26.9 - 27.1)</i>	<i>27.5 (27.4 - 27.5)</i>	<i>27.0 (26.9 - 27.0)</i>	<i>130,927</i>	<i>26.5 (26.4 - 26.6)</i>	<i>27.0 (27.0 - 27.1)</i>	<i>26.3 (26.3 - 26.4)</i>

Annual income over \$70,000 (n)	103,830 ^b				105,384 ^c			
	34,334	29.6%	26.3%	40.5%	28,477	28.0%	21.2%	33.4%
Sun exposure (hours / week)								
Less than 1 hour	5,635	1.7%	3.6%	6.6%	11,727	4.7%	7.5%	10.7%
1 - 4 hours	58,423	25.0%	46.5%	58.2%	92,732	58.7%	69.0%	70.4%
More than 4 hours	51,889	73.3%	49.9%	35.2%	30,253	36.6%	23.5%	18.9%
<i>Av. hours / week (age adjusted)</i>	115,947	<i>6.0 (5.9 - 6.0)</i>	<i>4.1 (4.0 - 4.1)</i>	<i>3.2 (3.2 - 3.2)</i>	134,712	<i>3.3 (3.3 - 3.4)</i>	<i>2.6 (2.6 - 2.6)</i>	<i>2.3 (2.3 - 2.4)</i>
Family history of cancer (n)								
Prostate cancer	13,595	13.3%	11.5%	10.0%	18,013	12.5%	12.9%	12.2%
Colo-rectal cancer	16,488	13.9%	13.8%	12.7%	20,418	14.4%	14.8%	13.7%
Lung cancer	11,993	8.6%	10.1%	9.4%	15,715	10.7%	11.4%	10.6%
Melanoma	9,420	9.2%	7.9%	7.1%	14,628	11.9%	10.6%	9.5%
Meat consumption (serves /wk)								
Less than 2 serves	15,044	8.7%	11.4%	14.3%	23,174	12.4%	16.2%	18.1%
2-3 serves	51,890	31.7%	41.8%	46.6%	65,296	37.2%	46.8%	49.4%
More than 3 serves	53,021	59.5%	46.8%	39.1%	49,681	50.4%	36.9%	32.4%
<i>Av. serves (age adjusted)</i>	119,955	<i>4.7 (4.7 - 4.8)</i>	<i>3.8 (3.8 - 3.8)</i>	<i>3.4 (3.4 - 3.4)</i>	138,151	<i>3.8 (3.8 - 3.9)</i>	<i>3.2 (3.2 - 3.2)</i>	<i>3.0 (3.0 - 3.0)</i>
Tannability (n)								
Get very tanned	39,036	36.6%	33.2%	30.4%	32,535	26.4%	23.1%	22.9%
Moderately tanned	52,277	43.7%	43.2%	42.7%	53,586	40.0%	38.4%	38.0%
Mildly/occasionally tan	22,211	14.9%	17.4%	19.7%	35,726	23.4%	25.6%	25.9%
Never tan / freckle	7,950	4.8%	6.2%	7.2%	17,863	10.1%	12.9%	13.2%

- a. 11% missing
- b. 16% data missing
- c. 26% missing

4.4.1 Mortality in men

Age-standardised mortality rate ratios and hazard ratios for each cancer are shown in Tables 2 and 3. The all cancer mortality rate ratio was significantly lower in farm men. The adjusted hazard ratio for all cancer was also lower in farm men, but not significantly so when controlling for additional risk factors. There were no significant differences in either the SMR or adjusted hazard ratio for men between cohorts for any of the individual cancers tested, with the exception of lung cancer. Rural non-farm men had a significantly higher lung cancer SMR but the adjusted hazard ratio was not significantly different to other men. Farm men had lower colorectal cancer and NHL mortality that was not significant; and non-significant elevations in prostate cancer. When adjusted for sun exposure and tannability, melanoma in farm men was higher, but not significantly so.

4.4.2 Mortality in women

Although not significantly different to other groups, farm women had the lowest SMR and adjusted hazard ratio for all cancers. Farm women also had the lowest SMR and adjusted hazard ratio for colorectal and lung cancer. In contrast, farm women had the highest adjusted hazard ratio for NHL controlling for age and other factors, though this was not significant. The SMR for breast cancer (SMR 60.49, 33.72 - 98.63) and melanoma (SMR=14.71, 0.37 - 81.95) in farm women was significantly lower than unity. Melanoma risk was not modelled because there were less than 5 cases within the farm group. However, the adjusted hazard ratio for breast cancer mortality in farm women was significantly lower than that for rural non-farm women (1.69, 1.00 – 2.87) controlling for age, family history, smoking and sun exposure.

Table 4.2: All cancers and selected cancer mortality in farm, rural non-farm and urban men of the 45 and Up Study cohort, 2006-2012

Cancer Type (ICD10) ^a & no. deaths	Cohort Residence n=123,882 p-years=522,121	Cases	Standardised Mortality Rate Ratio (95%CI)	Adjusted Hazard Ratio (95%CI)	Hazard ratios (95% CI) for variables remaining in final model (excl. age) / further notes
All neoplasms (C00 - D48) n= 4,207	Farm n= 9,281	193	80.5 (68.1 – 93.0)	1.00 (ref)	- Age^b - Alcohol consumption (> 5 days/wk) yes vs no HR= 0.84 (0.78 – 0.91) - Smoking status - never HR= 1.00 ref - past HR= 1.45 (1.33 – 1.57) - current HR= 2.76 (2.40 – 3.18) - Overweight/obesity status yes vs no HR= 0.89 (0.83 – 0.96) - Weekday sun exposure < 1 hr HR= 1.32 (1.10 – 1.59) 1 - 4 hrs HR= 1.00 ref > 4 hrs HR= 0.89 (0.83 – 0.97) - Annual household income over \$70,000 / year yes vs no HR= 0.75 (0.67 – 0.85)
	Rural non-farm n= 57,330	1,945	104.6 (99.9 – 109.3)	1.14 (0.96 – 1.36)	
	Urban n= 57,271	2,069	98.4 (94.1 – 102.6)	1.10 (0.92 – 1.32)	
Prostate (C61) n= 649	Farm	37	123.0 (78.8 – 167.2)	1.00 (ref)	- Age^b - Family history prostate cancer yes vs no HR= 1.95 (1.58 – 2.40) - Weekday sun exposure < 1 hr HR= 1.95 (1.38 – 2.77) 1 - 4 hrs HR= 1.00 ref > 4 hrs HR= 1.03 (0.87 – 1.22)
	Rural non-farm	288	103.8 (91.6 – 116.0)	0.89 (0.62 – 1.27)	
	Urban	324	94.7 (84.2 – 105.2)	0.81 (0.57 – 1.16)	
Colorectal (C18 - C21) n= 354	Farm	15	65.0 (34.7 – 109.8)	1.00 (ref)	- Age^b - Smoking status - never HR= 1.00 ref - past HR= 1.26 (1.01 – 1.59) - current HR= 1.83 (1.18 – 2.82)
	Rural non-farm	159	100.8 (84.9 – 116.7)	1.39 (0.82 – 2.37)	
	Urban	180	105.2 (89.6 – 120.8)	1.49 (0.87 – 2.52)	

Lung (C34) n= 716	Farm	33	76.5 (48.3 – 104.7)	1.00 (ref)	- Age^o - Smoking status - never HR= 1.00 ref - past HR= 4.95 (3.65 – 6.70) - current HR= 18.19 (12.89 – 25.68) - Alcohol risk (> 2 drinks/day) - yes vs no HR= 1.33 (1.06 – 1.67) - Alcohol risk (> 5 days/week) - yes vs no HR= 0.75 (0.61 – 0.93) - Annual household income over \$70,000 / year - yes vs no HR= 0.64 (0.47 – 0.86)
	Rural non-farm	366	112.5 (100.9 – 124.2)	1.14 (0.78 – 1.70)	
	Urban	317	90.4 (80.3 – 100.5)	0.98 (0.66 – 1.46)	
Melanoma (C43) n= 219	Farm	15	98.6 (53.8 – 164.6)	1.00 (ref)	- Age^o - Weekday sun exposure < 1 hr HR= 2.23 (1.18 – 4.21) 1 - 4 hrs HR= 1.00 ref > 4 hrs HR= 1.56 (1.15 – 2.10) - Tannability (when skin repeatedly exposed to sunlight in summer without protection) - very tan HR= 1.00 ref - moderate tan HR= 1.22 (0.83 – 1.78) - mild tan HR= 2.01 (1.39 – 3.16) - never tan/freckle HR= 2.69 (1.64 – 4.41)
	Rural non-farm	99	100.5 (80.4 – 120.6)	0.93 (0.52 – 1.68)	
	Urban	105	97.0 (78.2 – 115.8)	0.89 (0.49 – 1.61)	
Non-Hodgkins Lymphoma (C82 - C85) n= 149	Farm	7	76.3 (27.35 – 163.02)	1.00 (ref)	- Age^o - Alcohol risk (> 2 drinks/day) - yes vs no HR= 0.40 (0.21 – 0.75) - Annual household income over \$70,000 / year remained a non-significant confounder p=.21
	Rural non-farm	61	92.7 (69.15 – 116.28)	1.36 (0.54 – 3.41)	
	Urban	81	108.9 (84.79 – 132.92)	1.54 (0.61 – 3.85)	

a. ICD10 - International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

b. All models were significant for age (by five-year age groups), for which hazard ratios are not reported. All remaining variables significant to p<.01 level unless stated otherwise.

Table 4.3: All cancers and selected cancer mortality in farm, rural non-farm and urban women of the 45 and Up Study cohort, 2006-2012

Cancer Type (ICD10) ^a & no. deaths	Cohort Residence n=143,192 p-years=606,041	Cases	Standardised Mortality Rate Ratio (95%CI)	Adjusted Hazard Ratio (95%CI)	Hazard ratios (95% CI) for variables remaining in final model (excl. age) / other notes
All neoplasms (C00 - D48) n= 2,463	Farm n= 10,549	107	81.9 (63.5 – 100.2)	1.00 (ref)	- Age^b - Smoking status - never HR= 1.00 ref - past HR= 1.48 (1.33 – 1.65) - current HR= 2.63 (2.19 – 3.15) - Weekday sun exposure < 1 hr HR= 1.24 (1.04 – 1.47) 1 - 4 hrs HR= 1.00 ref > 4 hrs HR= 0.92 (0.81 – 1.04) - Annual household income over \$70,000 / year yes vs no HR= 0.84 (0.71 – 0.99)
	Rural non-farm n= 69,463	1,188	102.1 (96.3 – 108.0)	1.17 (0.92 – 1.50)	
	Urban n= 63,180	1,168	100.5 (96.64 – 106.30)	1.19 (0.93 – 1.53)	
Breast (C50) n= 424	Farm	18	60.5 (33.7 – 98.6)	1.00 (ref)	- Age^b - Family history breast cancer yes vs no HR= 1.81 (1.42 – 2.31) - Smoking status - never HR= 1.00 ref - past HR= 1.31 (1.06 – 1.61) - current HR= 1.17 (0.75 – 1.82) - Weekday sun exposure < 1 hr HR= 1.91 (1.27 – 2.87) 1 - 4 hrs HR= 1.67 (1.23 – 2.21) > 4 hrs HR= 1.00 ref
	Rural non-farm	215	105.6 (91.3 – 119.8)	1.69 (1.00 – 2.87)	
	Urban	191	99.6 (85.3 – 113.9)	1.56 (0.92 – 2.66)	
Colorectal cancer (C18 - C21) n= 246	Farm	9	65.7 (26.8 – 130.2)	1.00 (ref)	Age^b
	Rural non-farm	117	101.6 (83.0 – 120.2)	1.44 (0.73 – 2.83)	
	Urban	120	98.8 (80.8 – 116.7)	1.41 (0.71 – 2.79)	

Lung n= 716	Farm	19	78.4	1.00 (ref)	- Age^b - never HR= 1.00 ref - past HR= 4.12 (3.03 – 5.60) - current HR= 16.84 (11.81 – 24.02) - Weekday sun exposure < 1 hr HR= 1.67 (1.14 – 2.45) 1 - 4 hrs HR= 1.00 ref > 4hrs HR= 1.17 (0.88 – 1.56) - Annual household income over \$70,000 / year remained a non significant confounder p=.49
	Rural non-farm	202	101.4 (87.3 – 115.6)	1.04 (0.59 – 1.85)	
	Urban	194	102.3 (87.7 – 116.9)	1.14 (0.64 – 2.03)	
Melanoma (C43) n= 219	Farm	<5	14.7 (0.37 – 81.95)	1.00 (ref)	na
	Rural non-farm	39	108.6 (74.27 – 142.96)	na	
	Urban	34	100.1 (65.98 – 134.20)	na	
Non-Hodgkin Lymphoma (C82 - C85) n= 149	Farm	6	168.5 (55.7 – 378.1)	1.00 (ref)	- Age^b - Weekday sun exposure < 1 hr HR= 3.48 (190 – 6.36)* 1 - 4 hrs HR= 1.00 ref > 4hrs HR= 1.86 (1.13 - 3.08)*
	Rural non-farm	35	86.8 (57.6 – 115.9)	0.64 (0.25 – 1.66)	
	Urban	48	111.3 (79.3 – 143.3)	0.92 (0.36 – 2.36)	

- a. ICD10 - International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
- b. All models were significant for age and were stratified by five-year age groups, for which stratified hazard ratios are not reported. All remaining variables significant to p<.01 level unless stated otherwise.
- c. Not available due to small number of cases

4.4.3 Risk factors

Several risk factors remained significant in adjusted mortality models. In particular, smoking status remained significant in lung, breast and male colorectal cancer mortality models. The adjusted hazard ratio for current smoking in men was 18 times that of never smokers (HR= 18.19, 12.89 - 25.68); and 16 times that of never smokers amongst women (HR= 16.84, 11.81 - 24.02). Red meat consumption did not remain in final colorectal cancer models. However, household income did remain in lung cancer models. Adjusted hazard ratios for sun exposure were higher for minimal sun exposure than for high exposure and remained in final models for breast, lung cancer and NHL models in women; and in prostate cancer and melanoma mortality models for men.

4.5 Discussion

Results presented as an adjusted hazard ratio are considered more informative than SMR, since they account for additional risk factors other than age. However, SMR allows for more direct comparisons with previous studies that have used this measure; offers a gauge of the effect of age alone on mortality compared to when additional factors are considered; and is a general check for consistency of results using different outcome measures.

Whilst farm men had a significantly lower all cancer SMR, (four-fifths that of other men), differences in all cancer adjusted hazard ratios were less marked. Farm women had a similar SMR and adjusted hazard ratio, the former of borderline significance compared to all women, but not sub-groups. The most significant finding for specific cancers in this study was related to breast cancer mortality in farm women. This was significantly lower than unity controlling for age alone; and was also significantly lower than rural non-farm women, controlling for additional risk factors. Colorectal cancer mortality was lower in farm women than other groups, but not significantly so; and lung cancer mortality was similar between women when controlling for other factors. With less

than five deaths due to melanoma having occurred in the farm group, the finding for a significantly lower SMR in farm women needs to be considered with caution, as some instability in mortality ratios can arise using direct age-standardisation methods if case numbers are small.⁵² There were no significant differences in either mortality incidence or adjusted hazard ratios amongst men for any of the individual cancers tested, with the exception of the lung cancer SMR which was highest amongst rural non-farm men. Whilst not significant, there were slight elevations in prostate cancer and melanoma mortality risk in farm men, and reduced mortality for colorectal cancer and NHL mortality.

4.5.1 Risk factors

Previous studies have suggested higher rates of cancer mortality in rural areas may be attributed to higher risk alcohol consumption and smoking rates, less access or utilisation of health services; and educational, employment and income disadvantage.^{4, 6, 54-55} Disadvantaged groups have consistently been reported to have lower life expectancy, higher incidence, prevalence and risk factors for disease and greater rates of avoidable mortality.^{6 56} Rural non-farm residents in this cohort, particularly men, had the highest levels of risk in relation to smoking, obesity and income disadvantage. Smoking may be a particularly important issue amongst rural non-farm residents on lower incomes.

Alcohol consumption greater than 5 days/week was negatively associated with lung cancer mortality in men. Some benefit from the consumption of small amounts of alcohol by older adults on a daily basis, has been noted elsewhere.⁴⁵ Contrary to this, greater than two alcoholic drinks/day was positively associated with lung cancer mortality in the adjusted model. Variance inflation factors and standard errors in the base model were not excessive, but there may have been a degree of collinearity between this variable and others in the model. There was a general lack of evidence for

an association between excessive alcohol consumption and lung cancer in the literature, so findings for this risk factor should be considered with caution.⁴³

There was no evidence for an association between red meat consumption and colorectal cancer mortality in this study, contrary to evidence suggesting this elsewhere.⁵⁷ The higher level of weekday sun exposure in farm residents may reflect a more active outdoor lifestyle compared to the intermittent exposure of non-farm residents. Notably, the hazardous effects of minimal sun exposure in final models for NHL, breast and lung cancer in women; and melanoma and prostate cancer in men, are consistent with other studies suggesting links between sun exposure, Vitamin D levels and reduced risk in these cancers.⁵⁸⁻⁶² Very low sun exposure may also be a proxy indicator of an inactive indoor lifestyle with its own cancer health risks.

4.5.2 Mortality in farm residents

Whilst a few studies have reported increased all cancer risk in farmers,^{9-10, 63-64} most findings point to a lower overall cancer mortality.^{12-14, 16, 19, 24, 28, 31, 65} Higher sun exposure, or the more physical outdoor activity it represents, may have contributed to the lower all cancer mortality in farm residents. Compared to other occupational groups in Australia, farmers are older, work longer hours and are more likely to be self-employed, with lower disposable income, yet higher household wealth.⁴ These characteristics suggest a healthy worker effect may be at play amongst farm residents which has been acknowledged for farm cohorts elsewhere.^{12, 28, 31, 66} However, as opposed to an occupationally defined cohort, healthy worker bias for the farm residents' should be tempered by the presence of retirees, lifestyle farmers and family members. In addition, the cohort profile suggests urban residents overall had fewer lifestyle risk factors than farm residents - supporting the view that a healthy worker bias has been minimised in this cohort.

Whilst countless factors remain untested, the cohort profile suggests that outdoor activity may have had some role to play in all cancer risk being lower in farm residents; and perhaps, in relation

to lower (though not significant) colorectal cancer risk. Lower colorectal cancer in farmers has commonly been reported elsewhere, with greater physical activity and healthier diet postulated as possible explanations.^{12-14, 16, 24, 28, 31, 65, 67} The higher average red meat consumption in farmers found in this study remained within a moderate consumption range so does not necessarily contradict evidence on associations between high red meat consumption and colorectal cancer.⁴³ Questions remain as to why farm men had lower all cancer and colorectal cancer.

Most studies of breast cancer in farm women have found either reduced SMR^{12, 31} or no significant difference in mortality compared to others.^{27-28, 63, 68} The inverse relationship between breast cancer mortality and sun exposure in this study was unexpected, but whether acting for its own sake or as a proxy, the protective benefit of sun exposure for farm women clearly does not explain the remaining difference between groups in the final model. Breast cancer screening has been associated with a 15-30% reduction in mortality in women aged 50-69 years of age.⁶⁹ A previous study on cancer screening in the 45 and Up Study cohort found that rural women were more likely to have had a mammogram than urban women.⁷⁰ Participation in the national population-based breast cancer screening program (BreastScreen Australia), is also higher in regional compared to urban areas, although lowest in remote areas.⁷¹ Farm women may have been the driving force behind, and benefited most from, higher rates of breast screening in regional Australia.

Reduced lung cancer mortality in farmers has also been reported often, with lower smoking rates in farmers sometimes suggested as a contributing factor.^{12, 24-25, 28, 31, 72-73} Smoking accounted for a considerable portion of the difference in risk between groups in this study; and lung cancer mortality in farmers was less marked after controlling for this and other factors. There has also been suggestion that exposure to farm endotoxins has some protective benefit against lung cancer in farmers, but this was not assessed in our study.^{25, 73-76}

The melanoma mortality hazard ratio was slightly higher in farm men, but not significantly different to other rural non-farm and urban counterparts, when controlled for significantly higher levels of tannability and weekday sun exposure amongst farm residents. This suggests that regular, moderate sun exposure typical of farming may have played some protective role - although greater case numbers and follow-up time would be required to confirm this. Nonetheless, any mild protective benefit of occupational exposure does not necessarily contradict the importance of sun protection, especially against intense, periodic sunburn. Sun protection attitudes and behaviours have improved in recent years in Australia, which has one of the highest rates of melanoma in the world.⁷⁷

Slightly elevated prostate cancer mortality risk in farm men in this study, whilst not significant, was consistent with some other findings.^{24-25, 28} Others have reported significantly higher prostate cancer risk in farmers.^{9, 11-12, 14-16, 26, 66, 78-79} Pesticide exposures are a common explanation put forward, in a plethora of studies investigating pesticide-cancer associations that are outside the scope of this study. Notwithstanding this, a recent review suggests the overall evidence for increased prostate cancer mortality in farmers compared to others is not strong, partly due to limitations in study design.³²

Findings for NHL in this study were mixed and inconclusive; consistent with mixed findings in several studies.^{12, 16, 28} Whether this is due to changes in study measures, methods and limitations, or real reductions in mortality risk between farm residents and other groups remains to be seen. A number of large prospective cohort studies in development across the world may soon better answer such questions.^{12, 31, 80}

4.5.3 Limitations

There are some limitations of note regarding this study. Firstly, since the farm resident group represented only one-tenth of the overall cohort, the number of deaths over the follow-up period

for some cancers was relatively small. These issues were particularly apparent for lung and colorectal cancers, NHL and melanoma in the farm resident group. Low power for some analyses has resulted in relatively low precision and wide confidence intervals that affect the statistical significance of findings, potentially leading to a bias toward the null. Therefore, the discussion for these cancers is largely exploratory and focuses on trends suggested by point estimates. In this context, larger, more consistent differences between groups should be given most weight. Greater precision will be possible given a longer follow-up period, but trends in current results do provide some insight and direction for further work.

Secondly, the 45 and Up Study is not representative of the general NSW population 45 and over. However, its size and robust sampling methods have ensured an adequate number of rural and farm residents are able to be internally compared; and it is amongst the most representative large-scale cohort studies in the world.³⁴ A higher level of generalisability has also been suggested where associations between 45 and Up Study variables and items from linked data sets has occurred.⁸¹

Lastly, the definition of a 'farm resident' in this study was open to the respondent's interpretation of what constitutes a farm. This may have affected the representativeness of sub-groups and internal validity of some comparisons, contributing to a bias toward the null for some analyses. The number of people who live on non-commercial farms in NSW is also not known, nor what proportion of the farm resident group in this study that they comprise. Whilst small farm holdings make up the majority of farming enterprises in Australia, exposures may vary depending on whether commercial or recreational purposes are dominant.³³ Errors arising from misclassification however, are likely to dilute any effect farm 'exposure' might have on the outcome, leading to an underestimate of any relationship between farm residence and mortality. However, unlike many occupational studies, this study has been able to combine the benefits of a comparatively large sample size, with the ability to control for commonly known risk factors.

4.6 Conclusion

Farm, rural non-farm and urban residents differed in a range of health related characteristics. Whilst farm men had significantly lower all cancer SMR and rural non-farm men had significantly higher lung cancer SMR than other groups, there were no significant differences in this measure for NHL, colorectal, prostate cancer or melanoma. When controlling for additional risk factors, adjusted hazard ratios indicated no significant differences in the odds of mortality between farm, rural non-farm or urban men, either from all cancer or the other selected cancers.

The SMR for breast cancer and melanoma in farm women was significantly lower than unity, but there were no significant differences in this measure for all cancer, lung and colorectal cancer or NHL. Controlling for additional risk factors, farm women had a significantly lower adjusted hazard for breast cancer compared to rural non-farm women; but differences were not significant for other cancers.

Farm residents in this cohort had a lower mortality risk for all cancer than rural non-farm and urban residents, although results were not significant. Likewise, there were no significant differences in mortality risk for selected common cancers between resident groups after adjusting for a range of commonly known risk factors, with the exception of significantly lower breast cancer mortality in farm women.

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Chapter 5: Cancer incidence in farm, rural non-farm and urban residents in the 45 and Up Study cohort, New South Wales, Australia

This chapter is a manuscript that was prepared and submitted to *BMC Cancer* in October 2016 and is awaiting review

Depczynski J, Dobbins T, Armstrong B, Lower T. **Cancer incidence in farm, rural non-farm and urban residents in the 45 and Up Study cohort, New South Wales, Australia** . Manuscript prepared for peer review

5.1 Abstract

Background: It is not known if the incidence of common cancers in Australian farm residents is different to rural non-farm or urban residents. **Methods:** Data from farm, rural non-farm and urban participants of the 45 and Up Study cohort in New South Wales Australia, were linked with state cancer registry data for the years 2006 - 2009. Direct age-standardised incidence rate ratios were compared for all cancer, prostate, breast, colorectal cancer, melanoma and non-Hodgkin lymphoma (NHL). Proportional Hazards regression was used to generate incidence hazard ratios for each cancer type adjusted for relevant confounders. **Results:** Farm women had a significantly lower all cancer hazard ratio than for rural non-farm women; but lower all cancer risk in farm men compared to rural non-farm and urban counterparts was not significant. When rural non-farm and urban groups were combined, the all cancer adjusted hazard was significantly lower in both farm men and women. Confidence intervals did not exclude unity for differences in risk of prostate, breast, colorectal or lung cancers, NHL or melanoma but farm residents had considerably lower lung cancer risk than other residents after controlling for smoking and other factors. **Conclusions:** All cancer risk was significantly lower in farm residents compared to combined rural non-farm and urban groups. Farm women had a significantly lower all cancer adjusted hazard ratio than rural non-farm women. These differences appeared to be mainly due to lower lung cancer incidence in farm residents.

Keywords: Farm*, incidence, cancer, prostate, breast, melanoma, lung, colorectal, non-Hodgkin lymphoma

5.2 Introduction

Registration of all cancers, excluding non-melanoma skin cancers, is a legal requirement in all Australian States.¹⁻² The most commonly diagnosed cancers in Australia include prostate, colorectal, breast, lung cancer, melanoma and lymphoma.³ The distribution of these cancers varies across rural and urban areas. Between 2005-2009, incidence of prostate, colorectal, breast cancer, melanoma and non-Hodgkin lymphoma (NHL) was highest in inner regional areas and lung cancer highest in very remote areas.³

Cancer incidence is regularly reported by remoteness or accessibility to services,⁴ but not in a way that would distinguish those who do and do not live on farms. There is some limited information on mortality in male Australian farmers by occupation,⁵ however no information on cancer incidence for those who live on farms compared to others in rural areas or in cities in Australia, is known.

International studies have reported mixed findings on comparative cancer incidence between farmer and non-farmer groups. Most recent studies have reported reduced cancer incidence in farmers for all cancer, lung, breast and colorectal cancers.⁶⁻¹⁴ Meanwhile, most studies of prostate and lymphohaematopoietic cancers have reported neutral findings. However, around one fifth of lymphoma studies, a quarter of prostate cancer studies and almost half of myeloma and leukaemia studies report significant excesses of cancer incidence in farmer groups.^{6-8, 10-11, 14-26} Findings also vary by location, study design and degree of control for confounders which can affect comparability and the strength of conclusions drawn.²⁷⁻²⁸ The current study aims to add to this knowledge by comparing the incidence of common cancers in NSW farm, rural non-farm and urban residents.

5.3 Methods

This data linkage study was based on the 45 and Up Study cohort, consisting of 267,119 residents of NSW, Australia aged 45 years and over. The cohort data is maintained and managed by the Sax Institute, in collaboration with health agency partners. This study assessed cancer incidence for prostate, breast, colorectal, lung, melanoma and NHL, amongst farm, non-farm rural and urban residents, controlling for selected risk factors previously associated with cancer.

5.3.1 Sampling and recruitment

Between January 2006 and December 2009, eligible NSW individuals 45 years and over, were randomly sampled from the Australian Department of Human Services database, which provides near complete coverage of the NSW population. Persons aged 80 years and over and residents of rural and remote areas were oversampled by a ratio of 2:1. Subjects were mailed a questionnaire with consent form for follow-up and data linkage to routine health databases. An additional 0.5% of the final cohort comprised volunteers who contacted the Study hotline to participate. The overall response rate for sampled individuals was 17-18%; representing approximately 11% of the NSW population aged 45 years and over.²⁹ Further information about the study cohort is available from the *45 and Up Study* website.³⁰

5.3.2 Datasets and linkage

Participant records from the 45 and Up Study cohort provided information on residence (farm, rural or urban), age, family history of cancer, household income, screening practices, diet, obesity, sun exposure, smoking and alcohol consumption. Cancer incident cases amongst participants were identified through linkage to the NSW Cancer Registry (CCR) data, which contains records of all cases of cancer diagnosed in NSW residents, excluding non-melanoma skin cancers. Records were available for all new cancer notifications for the period 1st February 2006 (2006 was the first year in which 45 and Up Study participants were recruited) to 31st December 2009. Cancer type is derived

and coded according to International Statistical Classification of Diseases Ninth Edition (ICD-9) cancer groupings.³¹ Data quality control measures conducted by the CCR are reported elsewhere.² A small proportion of cancer cases were identified and coded only on receipt of the Cause of Death Unit Record File.^b For the year 2009 only, delays in receiving deaths data is likely to have caused under-reporting of <1% to 3.2% of cancer incident cases for the cancers of interest.³²

Data linkage was conducted by the NSW Centre for Health Record Linkage, using a probabilistic record linkage method. Detailed information on data linkage methods is available elsewhere.³³⁻³⁴ On reception of data, checks were undertaken for plausibility of dates and ranges, duplicate records, missing data, large numbers and illogical combinations of demographic, clinical variables and other unlikely combinations across datasets. Records with missing or invalid values for important variables of interest were excluded from analyses; and noted where these represented more than 10% of the available sample. Inconsistent data resulting from transcription errors or false positive linkages which could not be resolved by cross-checking across datasets were also removed from analysis. Description of all survey questions, response coding and sample checking procedures can be found in relevant data dictionaries.^{31, 35}

5.3.3 Definition of variables

‘Farm residents’ were defined as those who indicated that they lived in a ‘house on farm’ in the 45 and Up Study baseline questionnaire. Rural ‘non-farm’ and urban residents were further defined using the Accessibility/Remoteness Index of Australia (ARIA+) from postcode of residence at recruitment.^{4, 36} Those participants whose ARIA+ classification indicated they did not live in a ‘Major city’, excluding those who also specified that they lived in a ‘house on farm’, were defined as rural non-farm residents. The remaining ‘urban’ participants were those who lived in a ‘Major city’. Where

^b The Cause of Death Unit Record File (COD URF) is held by the NSW Ministry of Health Secure Analytics for Population Health Research and Intelligence and provided by the Australian Coordinating Registry for COD URF on behalf of Australian Registries of Births, Deaths and Marriages, Australian Coroners and the National Coronial Information System

ARIA+ was not recorded, allocation was determined by cross-checking with postcode of residence and distances to treating hospitals in a linked hospital dataset.

Characteristics of the cohort in relation to risk factors of interest, were age, family history of cancer and other factors categorised in accordance with current national health or workplace recommendations.³⁷⁻⁴³ These categories were: smoking status current, past, never; risky alcohol consumption >5 days/week, >2 drink/day; overweight and obesity status where Body Mass Index>25; red meat consumption <3-4<+ serves/week; and weekday sun exposure <1-4<+ hrs/week). Tannability, the response of participants skin when repeatedly exposed to sunlight in summer without protection (never, mild, moderate, very), was considered for melanoma models only. Household income was stratified to approximate levels above or below the 2006 average annual household income of \$70,000 in NSW in 2006.⁴⁴

5.3.4 Analytical procedures

Analyses were conducted using SAS 9.3™⁴⁵ software and Microsoft Excel 2007™.⁴⁶ For incidence ratios, person-years were calculated commencing from 1st February 2006 to censorship date, or the 14th day of the month of notification of a selected cancer. Cancer-specific subsets were used for each cancer type, to allow for persons registered with more than one type of cancer. Person-years for each participant were split across 5-year age-bands at risk, commencing from age at recruitment, to enable allocation of risk time to each age strata, as the person aged.⁴⁷⁻⁴⁸

Direct age-standardisation methods were used to calculate standardised incidence ratios (SIR). Variance of observed counts were based on the Normal approximation or the Poisson distribution where less than 30 events occurred within a resident group.⁴⁹ Consistent with *45 and Up Study* Collaboration recommendations, only internal comparisons between sub-groups within the cohort were made, with the reference population being the whole *45 and Up Study* cohort.²⁹ Standardised

incidence ratios were generated for all cancers and the cancers of interest, being prostate, breast, colorectal and lung cancers, melanoma and NHL.

Cox Proportional Hazards regression was used to model potential differences in incidence of selected cancers by cohort, controlling for risk factors.⁵⁰ Variables with univariate logrank p values < .25 were included in the base model. Interaction terms between variables in the base model and cohort were created and tested for effect modification. Models were progressively tested using backward elimination methods to the .05 level of significance; with non-significant variables also checked for confounding effects on the hazard ratios of cohort groups. Residual plots were examined to ensure assumptions of proportional hazards regression were met.

Sensitivity analyses were conducted using a smaller subset of data, where participants with prior cancer were removed and time to event for all records was limited to time since completing the questionnaire. However, results are primarily presented for the larger dataset, with reference to the comparison dataset as appropriate.

5.4 Results

Information from the 45 and Up Study survey questionnaire was available for 267,119 participants. Forty five records were removed for which dates of recruitment, age or gender information across datasets was incomplete or inconsistent. The remaining 267,074 participants were followed for 1,006,229 person-years (mean 3.8 years /person, max 3.9 years). Age-standardised incidence ratios and hazard ratios by gender for each cancer are shown in Tables 1 and 2. Summary characteristics of the cohort are available elsewhere.⁵¹

Table 5.1: Cancer incidence and hazard ratios of farm, rural non-farm and urban men, 2006-2009

Cancer Type (ICD9) ^a No. incident cases / Total person-years	Cohort Residence n=123,882	Cases	Standardised Incident Rate Ratio (95%CI)	Adjusted Hazard Ratio (95%CI)	Hazard ratios (95% CI) for variables remaining in final model (excl. age) / other notes
All malignant neoplasms (excl. NMSC)^b	Farm n= 9,281	496	91.7 (83.1 – 100.3)	1.00 (ref)	- Age^b - Smoking status - never HR= 1.00 ref - past HR= 1.09 (1.04 – 1.15) - current HR= 1.11 (0.99 – 1.23) - Annual household income \$70,000 and over yes vs no HR= 0.92 (0.86 – 0.98)
C00 - C98 (excl. C44)	Rural non-farm n= 57,330	3,814	102.9 (99.6 – 106.1)	1.09 (0.99 – 1.21)	
n= 7,957 P- years= 463,068	Urban n= 57,271	3,647	98.0 (94.8 – 101.2)	1.08 (0.97 – 1.20)	
Prostate (C61)	Farm	252	98.5 (85.7 – 111.3)	1.00 (ref)	- Age^b - Family history prostate cancer yes vs no HR= 1.83 (1.68 – 1.99) - Smoking status - never HR= 1.00 ref - past HR= 0.96 (0.89 – 1.02) - current HR= 0.80 (0.68 – 0.93)
n= 3,647 P- years= 470,298	Rural non-farm	1,780	102.8 (98.0 – 107.6)	1.06 (0.93 – 1.21)	
	Urban	1,615	97.2 (92.4 – 102.0)	1.01 (0.88 – 1.16)	
Colorectal (C18 - C21)	Farm	62	100.3 (72.2 – 128.5)	1.00 (ref)	- Age^b - Family history colorectal cancer yes vs no HR=1.31 (1.12 – 1.54) - Smoking status - never HR= 1.00 ref - past HR= 1.30 (1.14 – 1.48) - current HR= 1.26 (0.96 – 1.66)
n= 1,040 P- years= 475,307	Rural non-farm	512	106.0 (96.7 – 115.3)	1.12 (0.86 – 1.46)	
	Urban	466	95.0	1.02	

Lung (C34) n= 426 P- years= 476,776	Farm	19	71.4 (39.7 – 116.1)	1.00 (ref)	- Age^d - Family history lung cancer yes vs no HR= 1.46 (1.06 – 2.01) - Smoking status never HR= 1.00 ref past HR= 6.52 (4.31 – 9.87) current HR= 18.77 (11.72 – 30.05) - Annual household income over \$70,000 Yes vs no HR= 0.48 (0.32 – 0.73)
	Rural non-farm	207	105.1 (90.6 – 119.5)	1.19 (0.70 – 2.02)	
	Urban	200	95.6 (82.2 – 109.1)	1.22 (0.71 – 2.09)	
Melanoma (C43) n= 1,051 P- years= 475,264	Farm	75	108.5 (81.3 – 135.6)	1.00 (ref)	- Age^d - Family history melanoma yes vs no HR=2.06 (1.71 – 2.47) - Smoking status never HR=1.00 ref past HR= 0.83 (0.73 – 0.94) current HR= 0.56 (0.40 – 0.79) - Tannability (response of skin repeatedly exposed to sunlight in summer without protection) very tan HR=1.00 ref moderate tan HR=1.52 (1.29 – 1.80) mild tan HR= 2.16 (1.80 – 2.59) never tan/freckle HR= 2.39 (1.90 – 3.01)
	Rural non-farm	491	101.6 (92.5 – 110.6)	0.90 (0.71 – 1.15)	
	Urban	485	98.4 (89.5 – 107.2)	0.87 (0.68 – 1.11)	
Non-Hodgkin Lymphoma (C82 - C85) n= 269 P- years= 476,768	Farm	14	64.6 (34.8 – 109.2)	1.00 (ref)	- Age^b - Annual household income \$70,000 / year and over and red meat consumption remained as non-significant confounders
	Rural non-farm	117	93.7 (76.6 – 110.8)	0.88 (0.50 – 1.55)	
	Urban	138	106.5 (88.5 – 124.4)	0.96 (0.56 – 1.73)	

a. ICD9 - International Statistical Classification of Diseases, Ninth Revision

b. All models included age stratified by five-year age-bands at risk. Age remained significant in all models, but stratified hazard ratios are not reported

Table 5.2: Cancer incidence and hazard ratios of farm, rural non-farm and urban women 2006-2009

Cancer Type (ICD9) ^a No. incident cases / Total person-years	Cohort Residence n=143,192	Cases	Standardised Incident Rate Ratio (95%CI)	Adjusted Hazard Ratio (95%CI)	Hazard ratios (95% CI) for variables remaining in final model (excl. age) / other notes
All malignant neoplasms (excl. NMSC)^b	Farm n= 10,549	107	81.9 (63.5 – 100.2)	1.00 (ref)	- Age^b - Overweight & obesity status yes vs no HR= 1.06 (1.00 – 1.13)
C00 - C98 (excl. C44)	Rural non-farm n= 69,463	1,188	102.1 (96.3 – 108.0)	1.14 (1.01 - 1.29)	Smoking status never HR= 1.00 ref past HR= 1.19 (1.12 – 1.27) current HR= 1.11 (0.98 – 1.25)
n= 5,011 P- years= 513,232	Urban n= 63,180	1,168	100.5 (96.6 – 106.3)	1.12 (0.99 – 1.27)	
Breast (C50)	Farm	117	87.0 (69.6 – 104.5)	1.00 (ref)	- Age^b - Family history breast cancer yes vs no HR= 1.58 (1.39 – 1.79)
n= 1,762 P- years= 548,760	Rural non-farm	863	100.5 (93.8 – 107.3)	1.06 (0.87 – 1.29)	Overweight & obesity status yes vs no HR=1.13 (1.03 – 1.25)
	Urban	782	101.6 (94.5 – 108.8)	1.06 (0.86 – 1.29)	- Smoking status never HR= 1.00 ref past HR= 1.11 (1.00 – 1.23) current HR= 0.78 (0.62 – 0.98) - Weekday sun exposure < 1 hr HR= 1.33 (1.10 – 1.61) 1 - 4 hrs HR= 1.12 (0.99 – 1.27) > 4 hrs HR= 1.00 ref
Colorectal (C18 - C21)	Farm	48	97.3 (33.4 – 128.3)	1.00 (ref)	- Age^b - Family history colorectal cancer yes vs no HR= 1.27 (1.07 – 1.52)
n= 815 P- years=550,743	Rural non-farm	411	104.7 (94.9 – 114.9)	1.03 (0.76 – 1.40)	Smoking status never HR= 1.00 ref past HR= 1.21 (1.06 – 1.41) current HR= 0.93 (0.65 – 1.33)
	Urban	356	95.4 (85.4 – 105.5)	0.95 (0.70 – 1.29)	

Lung (C34) n=300 P- years= 551,870	Farm	7	48.1 (8.8 – 117.8)	1.00 (ref)	- Age^o - Smoking status - never HR= 1.00 ref - past HR= 3.58 (2.54 – 5.07) - current HR= 9.51 (6.17 – 14.65) - Annual household income \$70,000 and over / yr remained as a non-significant confounder (p=.09)
	Rural non-farm	157	106.3 (89.5 – 123.0)	1.82 (0.80 – 4.15)	
	Urban	136	101.8 (84.5 – 119.1)	1.83 (0.80 – 4.22)	
Melanoma (C43) n=622 P- years= 551,022	Farm	41	103.3 (65.4 – 141.2)	1.00 (ref)	- Age^o p<.01 - Family history melanoma - yes vs. no HR= 2.08 (1.68 – 2.57) - Weekday sun exposure < 1 hr HR= 1.20 (0.89 – 1.61) 1 - 4 hrs HR= 1.00 ref > 4 hrs HR= 1.32 (1.09 – 1.60) - Tannability (response of skin repeatedly exposed to sunlight in summer without protection) - very tan HR= 1.00 ref - moderate tan HR= 1.46 (1.13 – 1.89) - mild tan HR= 1.76 (1.35 – 2.29) - never tan/freckle HR= 2.32 (1.74 – 3.09)
	Rural non-farm	332	110.3 (98.3 – 122.2)	1.11 (0.79 – 1.56)	
	Urban	249	89.6 (78.4 – 100.8)	0.95 (0.67 – 1.34)	
Non-Hodgkin's Lymphoma (C82 - C85) n= 211	Farm	13	122.4 (55.5 – 210.0)	1.00 (ref)	- Age^o - Annual household income \$70,000 and over / yr remained a non-significant confounder (p=.62)
	Rural non-farm	93	91.8 (73.0 – 110.6)	1.15 (0.55 – 2.39)	
	Urban	105	108.8 (87.8 – 130.0)	1.30 (0.62 – 2.70)	

a. ICD9 - International Statistical Classification of Diseases, Ninth Revision

b. All models included age stratified by five-year age-bands at risk. Age remained significant in all models, but stratified hazard ratios are not reported

5.4.1 Cancer incidence

The age-standardised all cancer incidence ratio and the adjusted hazard of cancer diagnosis in farm men was almost 10% lower than in rural non-farm and urban men, although not significant between subgroups. However, when rural non-farm and urban men are combined as a group to increase precision, the hazard ratio was 1.08 (1.01-1.17) compared to farm men. Farm men also had the lowest lung cancer and highest melanoma incidence, but these were not significantly different to either the rural non-farm or urban groups. There was little difference between farm men and other groups for NHL, prostate or colorectal cancer incidence.

All cancer incidence was lowest in farm women. The SIR was 20% lower than either of the other groups, although differences were not significant. However, when controlling for other factors, the all cancer adjusted hazard ratio for farm women was significantly lower than that for rural non-farm, but not urban women. Similar to men, the hazard ratio relative to a combined rural non-farm and urban group was 1.13 (1.04-1.23), significantly higher than that of farm women. There were no significant differences in SIR or adjusted hazard ratios between residence groups for women, for any of the individual cancers tested. However, whilst confidence intervals did not exclude unity, both the incidence and adjusted hazard of lung cancer in farm women were around half that of other women. Results for the sensitivity analyses were generally consistent with findings for the main analyses for both men and women.

5.4.2 Potential risk factors

Farm residents in this cohort were younger than rural non-farm and urban residents, with age controlled for in all adjusted hazard models. Family history was associated with most of the selected cancers, although this information was not available for NHL. Smoking status was significantly associated with lung cancer, with the adjusted hazard ratio for current smoking 18 times that of never smokers in men; and 9 times that of never smokers amongst women. In contrast, current

smoking was negatively associated with prostate cancer and melanoma in men; as was income for lung and all cancer in men. Tannability was negatively associated with melanoma in both genders. For women, higher sun exposure appeared weakly protective against breast cancer, but increased risk for melanoma. Overweight and obesity were associated with greater likelihood of both all cancer and breast cancer in women. Income and red meat consumption were non-significant confounders for some cancers; whilst alcohol consumption was not associated with any of the cancers of interest.

5.5 Discussion

Adjusted hazard ratios and SIR are both discussed, but it is recommended more weight be given to the adjusted hazard ratios, as they control for additional risk factors. Age-standardised all cancer incidence and adjusted hazard of a cancer diagnosis was lower in farm men, but differences were not statistically significant when compared to rural non-farm or to urban men separately. Farm women had non-significantly lower all cancer incidence; but the adjusted hazard of a cancer diagnosis in farm women was significantly lower than rural non-farm women, controlling for other factors. There were no significant differences in either the age-standardised incidence or adjusted hazard ratio between cohorts for any of the individual cancers tested; although the incidence and adjusted hazard of lung cancer in farm women was around half that of other women. In this study, smoking had the highest relative risk of all risk factors in adjusted hazard models, having a particularly strong association with lung cancer. However, men who were current smokers were half as likely to be diagnosed with melanoma; and women with higher weekday sun exposure were least likely to be diagnosed with breast cancer.

5.5.1 Incidence

Consistent with the direction of our findings, most reviews and recent studies have reported reduced all cancer incidence in farmers.^{8, 10-14, 52-53} Some have attributed decreased cancer risk in

farmers to a 'healthy worker' effect; a phenomenon observed when comparing occupational groups with the general population, that by nature exclude those who are unable to work for health reasons.^{8, 10, 54-55} Most farm businesses in Australia are family operations with ongoing generational commitment resulting in older farmers continuing to work into and past normal retirement age.⁵⁶ However, this study compared groups on a residential basis which may have ameliorated occupational bias to some extent. Smoking, alcohol and income-related indicators presented elsewhere, were generally more favourable in this cohort amongst urban residents.⁵¹ Greater physical activity in farm residents in this cohort was suggested by their higher weekday sun exposure⁵¹ and may have been a contributing factor to lower all cancer incidence, as has been suggested elsewhere.⁵³

Despite the small number of farm resident cases in this study for men and women, the lower lung cancer incidence and relative risk in farm residents support data from other studies reporting on farmers.⁶⁻¹³ Lower smoking rates in farmers have been suggested as the relevant factor, but this was not the case in this cohort, considering that urban men had lower current smoking rates⁵¹; and lower cancer incidence in farmers remained even after controlling for smoking in the analyses. Exposure to farm animals and environmental endotoxins have also been reported as possible explanations for lower lung cancer incidence in farmers, however this was not assessed as part of this study.⁵⁷⁻⁶⁰

There was little discernible difference between groups in our study for the other selected cancers. Most recent studies of colorectal cancer in farmers have reported reduced incidence or risk in farmers. These have predominantly been large occupational cohort studies with a minimum follow-up of ten years.⁸⁻¹⁴ Four of these studies reported reduced risk of breast cancer in farm women, as did two other studies of similar design.⁶⁻⁷ The only recent reports of excess breast and colorectal cancer in farm groups, have been from smaller case-control studies.⁶¹⁻⁶²

Findings for breast, melanoma and prostate cancer in farmers have been mixed, with several reporting no significant differences between farm and non-farm groups.^{8, 10-13, 63-66} Neutral findings have been reported for the majority of comparative studies of lymphoma in farmers published in the ten years to 2013.^{8, 10-14, 20, 22, 24, 67-73} However, more recent case-control studies have reported an excess of lymphomas in farm groups,^{15, 17-18, 61} similar to earlier reviews of case control studies.^{52-53, 74}

One prominent meta-analysis highlighted the inconsistencies of results brought about by variations in study design, risk measures, farmer definitions and geographic location.⁵² A positive bias can occur in studies that use proportionate measures of risk in populations where the overall number of cases is small; and in case-control studies with non-population based controls.⁵² This could help explain why such studies tend to report increased prostate cancer and NHL risk in farmers, compared to cohort studies, which more often report neutral or reduced risk.⁵² This effect was confirmed in a more recent review of prostate cancer risk in farmers published in 2014.²⁸ Since then, two more studies reflecting these issues have reported opposing results;^{6, 25} and a new meta-analysis limited to case-control studies, not unexpectedly reported higher risk in farmers.¹⁵ In contrast, negative bias can be an issue in large cohort or occupational studies, if there is limited information about possible confounders.

5.5.2 Risk factors

Other studies have suggested increased cancer incidence in rural areas may be attributed to higher smoking and alcohol use, lower access to or utilisation of health services; and employment or income disadvantage.⁷⁵⁻⁷⁶ A greater proportion of rural non-farm residents in this cohort were current smokers and had lower incomes.⁵¹ However, as expected when controlling for these factors, there was no evidence of a difference in lung cancer risk between rural non-farm and urban men in the adjusted model. In addition, whilst findings were not significant, these risk factors did not

explain the lower likelihood of lung cancer in farm residents compared to the other groups. Confirmation of this effect with a larger farm resident sample is warranted.

Nevertheless, findings support what is already known about the hazardous effect of smoking upon lung cancer and all cancer; and health promotion priorities of Australian health systems toward prevention and reduction of tobacco use, especially amongst groups with a higher prevalence of smoking.⁷⁷ The negative associations between smoking and breast cancer, prostate cancer and melanoma in men may have been an artefact of the relatively short follow-up period. However, a recent meta-analysis has also reported negative links between smoking and prostate cancer incidence and unclear links to breast cancer.⁷⁸⁻⁷⁹ There have been reports of negative associations between smoking and melanoma - although the biological mechanisms are unclear.⁸⁰⁻⁸² Overall, the negative associations with smoking had a relatively minor impact upon the relative patterns of risk between resident groups.

A related study of cancer mortality risk in this cohort, found that compared to very low exposure, weekday sun exposure of 1- 4 hrs was protective against NHL, prostate, breast, melanoma and lung cancer mortality.⁵¹ This was also the case for melanoma incidence in this study. Others have similarly reported inverse melanoma risk with occupational or weekday patterns of sun exposure, as opposed to the more intermittent patterns giving rise to sunburn that raises melanoma risk.⁸³ However, 4 hours+ sun exposure was most protective against breast cancer. Other studies have also suggested links between sun exposure, Vitamin D levels and reduced risk of breast cancer.⁸⁴⁻⁸⁶ However, it is also possible that moderate sun exposure represented greater relative health and outdoor physical activity, which is promoted in Australian cancer prevention guidelines.³⁷

Several studies have explored positive associations between cancer incidence and farm environmental exposures, such as pesticides. However, these are outside the scope of this study, as

they do not generally compare farm and non-farm groups; and farm exposure information was not available in this dataset.

The negative significant association between lung cancer in men and income, is consistent with findings elsewhere, relating to higher levels of smoking in lower socio-economic groups.⁸⁷ Overweight and obesity was associated with breast cancer in this study, also consistent with reports in the health literature.³⁷ However, contrary to evidence of links between alcohol consumption and breast, colorectal and other cancers, this was not associated with any of the selected cancers in this cohort.³⁷

5.5.3 Limitations

There are a number of limitations in this study that may have affected the results. Firstly, the relatively short period of follow-up and subsequent small number of incident cancers for the period for which data were available, especially in the farm group, resulted in low power and wide confidence intervals for some analyses. This may have impacted upon the significance of findings, leading to a bias toward the null. Discussion of results with confidence intervals that include unity should be considered exploratory; and larger, consistent differences given more weight. Nevertheless, results still offer insight into potential differences and guidance for further work.

In order to maximize both cases numbers and follow-up time, this study consisted of all records of cancer for participants who could potentially receive a diagnosis of cancer at any time in the 2006-2009 study period; that is, cancer diagnosis in some participants could have preceded their enrolment in the 45 and Up Study. This may have effected behavioural risk factors at recruitment (e.g. smoking). However, such an effect is likely to be non-differential relating to residence; and results of the sensitivity analyses were consistent with and support the main findings.

The *45 and Up Study* cohort, whilst a large cohort with robust sampling methods, is not necessarily representative of the population of NSW aged 45 and over.²⁹ However, little evidence of bias was observed in associations between risk factors and disease seen in the 45 and Up Study population.⁸⁸ Finally, the definition of a 'farm resident' in this study was also open to respondents' interpretation of 'farm', which could include small holdings used for commercial, recreational or both purposes. Exposures could be quite different depending on which of these purposes was dominant. Farm exposure differences and errors arising from misclassification of residence, are likely to have lessened any differences between resident groups, but not likely to have systematically affected non-residential risk factors. Therefore, any potential bias is likely toward the null and an underestimation of a relationship between farm residence and cancer incidence.

5.6 Conclusion

This study is the first to examine differences in incidence of cancer between farm, rural non-farm and urban residents in Australia. Controlling for a range of risk factors, farm women had significantly lower odds of all cancer than rural non-farm women. Farm men had lower all cancer risk, but this was not statistically significant compared to rural non-farm and urban men. When combining rural non-farm and urban groups, the all cancer adjusted hazard was significantly lower in both farm men and women, due to increased precision.

Differences between groups in the risk of prostate, breast, colorectal or lung cancers, NHL or melanoma, were not significant after controlling for commonly known risk factors. However, notwithstanding small case numbers and a lack of statistical significance, farm women had around half the odds of other women in being diagnosed with lung cancer, controlling for smoking and other factors. Differences in all cancer risk appeared to be mainly due to lower lung cancer incidence in farm residents.

5.7 Acknowledgements

The *45 and Up Study* is managed by the Sax Institute in collaboration with major partner Cancer Council NSW; and partners: the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; NSW Government Family & Community Services – Ageing, Carers and the Disability Council NSW; and the Australian Red Cross Blood Service; and the many thousands of people participating in the 45 and Up Study.

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5.8 Appendix

Table 5.3: Comparison of case numbers and adjusted hazard ratios for main analyses compared to sensitivity analyses for incidence of selected cancers in men

Cancer Type (ICD9) ^a	Cohort residence n=123,882	Newly diagnosed cases registered in NSW CR 2006-2009 (main analyses)			Newly diagnosed cases registered in NSW CR from recruitment to 2009 and excluding any self-reported prior cancer (sensitivity analyses)		
		Cancer cases	Adjusted hazard ratio (95%CI)	Adjusted hazard ratios for variables in final model	Cancer cases	Adjusted hazard ratio (95%CI)	Adjusted hazard ratios for variables in final model
Prostate (C61)	Farm	252	1.00 (ref)	- Age^b - Family history prostate cancer yes vs no HR= 1.83 (1.68 - 1.99)	105	1.00 (ref)	- Age^b - Family history prostate cancer yes vs no HR= 1.85 (1.60 – 2.14)
	Rural non-farm	1,780	1.06 (0.93 – 1.21)	- Smoking status - never HR= 1.00 ref - past HR= 0.96 (0.89 - 1.02) - current HR= 0.80 (0.68 - 0.93)	653	1.01 (0.81 – 1.25)	- Smoking status - never HR= 1.00 ref - past HR= 0.86 (0.78 – 0.97) - current HR= 0.62 (0.47 – 0.82)
	Urban	1,615	1.01 (0.88 – 1.16)		618	1.05 (0.84 – 1.31)	- Sun exposure hrs/day < 1 hr HR= 1.00 ref 1– 4 hrs HR= 1.35 (0.95 – 1.91) > 4 hrs HR= 1.54 (1.01 – 2.18)
Colorectal (C18 - C21)	Farm	62	1.00 (ref)	- Age^b - Family history colorectal cancer yes vs no HR=1.31 (1.12 - 1.54)	22	1.00 (ref)	- Age^b - Alcohol risk (>2 drinks/day) yes vs no HR= 1.27 (1.00 – 1.60)
	Rural non-farm	512	1.12 (0.86 – 1.46)	- Smoking status - never HR= 1.00 ref - past HR= 1.30 (1.14 - 1.48) - current HR= 1.26 (0.96 - 1.66)	178	0.99 (0.73 – 1.32)	- Smoking status - never HR= 1.00 ref - past HR= 1.33 (1.06 – 1.68) - current HR= 1.59 (1.05 – 2.39)
	Urban	466	1.02 (0.78 – 1.33)		166	0.83 (0.61 – 1.13)	
Lung (C34)	Farm	19	1.00 (ref)	- Age^b - Family history lung cancer yes vs no HR= 1.46 (1.06 - 2.01)	7	1.00 (ref)	- Age^b - Alcohol risk (>2 drinks/day) yes vs no HR= 1.51 (1.08 – 2.12)
	Rural non-farm	207	1.19 (0.70 – 2.02)	- Smoking status - never HR= 1.00 ref - past HR= 6.52 (4.31 - 9.87) - current HR= 18.77 (11.72 - 30.05)	112	1.72 (0.75 – 3.94)	- Smoking status - never HR= 1.00 ref - past HR= 8.23 (4.00 – 16.97) - current HR= 36.23 (16.90 – 77.69)
	Urban	200	1.22 (0.71 – 2.09)	Annual household income over \$70,000 yes vs no HR= 0.48 (0.32 - 0.73)	89	1.53 (0.66 – 3.54)	Annual household income over \$70,000 /yr yes vs no HR= 0.46 (0.25 – 0.86)

Melanoma (C43)	Farm	75	1.00 (ref)	- Age^b - Family history melanoma yes vs no HR= 2.06 (1.71 - 2.47) - Smoking status - never HR= 1.00 ref - past HR= 0.83 (0.73 - 0.94) - current HR= 0.56 (0.40 - 0.79) - Tannability (response of skin repeatedly exposed to sunlight in summer without protection) - very tan HR= 1.00 ref - moderate tan HR= 1.52 (1.29 - 1.80) - mild tan HR= 2.16 (1.80 - 2.59) - never tan/freckle HR= 2.39 (1.90 - 3.01)	26	1.00 (ref)	- Age^b - Family history melanoma yes vs no HR=1.83 (1.31 - 2.57) - Smoking status - never HR= 1.00 ref - past HR= 0.78 (0.64 - 0.97) - current HR= 0.58 (0.34 - 0.99) - Tannability (response of skin repeatedly exposed to sunlight in summer without protection) - very tan HR= 1.00 ref - moderate tan HR= 1.94 (1.46- 2.57) - mild tan HR= 2.37 (1.72 - 3.26) - never tan/freckle HR= 2.69 (1.80 - 4.03)
	Rural non-farm	491	0.90 (0.71 – 1.15)		180	1.00 (0.66 – 1.52)	
	Urban	485	0.87 (0.68 – 1.11)		174	0.94 (0.62 – 1.43)	
Non-Hodgkin Lymphoma (C82 - C85)	Farm	14	1.00 (ref)	- Age^b - Annual household income \$70,000/yr and over (p=.37) and red meat consumption (p=.12) remained as non-significant confounders	5	1.00 (ref)	- Age^b - Annual household income \$70,000/yr and over (p=.14) and smoking status (p=.10) remained as non-significant confounders
	Rural non-farm	117	0.88 (0.50 – 1.55)		44	0.89 (0.35 – 2.29)	
	Urban	138	0.96 (0.56 – 1.73)		54	1.05 (0.41 – 2.67)	

a. ICD9 - International Statistical Classification of Diseases, Ninth Revision

b. All models included age stratified by five-year age-bands at risk. Age remained significant in all models, but stratified hazard ratios are not reported

Table 5.4: Comparison of case numbers and adjusted hazard ratios for main analyses compared to sensitivity analyses for incidence of selected cancers in women

Cancer Type (ICD9) ^a	Cohort residence n=123,882	Newly diagnosed cases registered in NSW CR 2006-2009 (main analyses)			Newly diagnosed cases registered in NSW CR from recruitment to 2009 and excluding cases with self-reported prior cancer (sensitivity analyses)		
		Cancer cases	Adjusted hazard ratio (95%CI)	Adjusted hazard ratios for variables in final model	Cancer cases	Adjusted hazard ratio (95%CI)	Adjusted hazard ratios for variables in final model
Breast (C50)	Farm	117	1.00 (ref)	- Age^b - Family history breast cancer yes vs no HR= 1.58 (1.39 – 1.79)	56	1.00 (ref)	- Age^b - Alcohol risk (>2 drinks/day) yes vs no HR=1.49 (1.12 - 1.97)
	Rural non-farm	863	1.06 (0.87 – 1.29)	- Overweight & obesity status yes vs no HR= 1.13 (1.03 – 1.25) - Smoking status never HR= 1.00 ref past HR= 1.11 (1.00 – 1.23) current HR= 0.78 (0.62 – 0.98)	351	0.99 (0.73 – 1.32)	Weekday sun exposure < 1 hr HR= 1.00 ref 1- 4 hrs HR= 0.75 (0.58 – 0.97) > 4 hrs HR= 0.72 (0.54 – 0.97)
	Urban	782	1.06 (0.86 – 1.29)	Weekday sun exposure < 1 hr HR= 1.33 (1.10 – 1.61) 1 - 4 hrs HR= 1.12 (0.99 – 1.27) > 4 hrs HR= 1.00 ref	269	0.83 (0.61 – 1.13)	
Colorectal (C18 - C21)	Farm	48	1.00 (ref)	- Age^b - Family history colorectal cancer yes vs no HR=1.27 (1.07 - 1.52)	22	1.00 (ref)	- Age^b - Smoking status never HR= 1.00 ref past HR= 1.58 (1.25 - 1.99) current HR= 1.21 (0.70 – 2.10)
	Rural non-farm	411	1.03 (0.76 – 1.40)	Smoking status never HR= 1.00 ref past HR= 1.21 (1.06 - 1.41) current HR= 0.93 (0.65 - 1.33)	150	0.85 (0.54 – 1.35)	
	Urban	356	0.95 (0.70 – 1.29)		134	0.81 (0.51 – 1.30)	
Lung (C34)	Farm	7	1.00 (ref)	- Age^b - Smoking status never HR= 1.00 ref past HR= 3.58 (2.54 - 5.07) current HR= 9.51 (6.17 - 14.65)	<5	1.00 (ref)	- Age^b - Smoking status never HR= 1.00 ref past HR= 3.38 (2.01 - 5.67) current HR= 16.72 (9.43 – 29.65)
	Rural non-farm	157	1.82 (0.80 – 4.15)	Annual household income \$70,000/ yr and over remained a non-significant confounder (p=.09)	79	1.76 (0.55 – 5.67)	
	Urban	136	1.83 (0.80 – 4.22)		71	1.95 (0..60 – 6.31)	

Melanoma (C43)	Farm	41	1.00 (ref)	- Age^b p<.01 - Family history melanoma yes vs no HR=2.08 (1.68 – 2.57) - Weekday sun exposure < 1 hr HR= 1.20 (0.89 – 1.61) 1- 4 hrs HR= 1.00 ref > 4 hrs HR= 1.32 (1.09 – 1.60) - Tannability (response of skin repeatedly exposed to sunlight in summer without protection) - very tan HR= 1.00 ref - moderate tan HR= 1.46 (1.13 – 1.89) - mild tan HR= 1.76 (1.35 – 2.29) - never tan/freckle HR= 2.32 (1.74 – 3.09)	23	1.00 (ref)	- Age^b p<.01 - Family history melanoma yes vs no HR= 1.60 (1.09 – 2.34) - Weekday sun exposure < 1 hr HR= 1.04(0.63 – 1.73) 1-4 hrs HR= 1.00 ref > 4hrs HR= 1.42 (1.05 – 1.94) - Tannability (response of skin repeatedly exposed to sunlight in summer without protection) - very tan HR= 1.00 ref - moderate tan HR= 2.71 (1.67 – 4.40) - mild tan HR= 2.74 (1.65 – 4.56) - never tan/freckle HR= 4.15 (2.43 – 7.09)
	Rural non-farm	332	1.11 (0.79 – 1.56)		122	0.77 (0.49 – 1.23)	
	Urban	249	0.95 (0.67 – 1.34)		83	0.63 (0.39 – 1.02)	
Non-Hodgkin Lymphoma (C82 - C85)	Farm	13	1.00 (ref)	- Age^b - Annual household income \$70,000 and over remained a non-significant confounder (p=.62)	<5	1.00 (ref)	Age^b
	Rural non-farm	93	1.15 (0.55 – 2.39)		32	1.45 (0.44 – 4.75)	
	Urban	105	1.30 (0.62 - 2.70)		37	1.81 (0.56 – 5.91)	

a. ICD9 - International Statistical Classification of Diseases, Ninth Revision

b. All models included age stratified by five-year age-bands at risk. Age remained significant in all models, but stratified hazard ratios are not reported

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Chapter 6: Stage of diagnosis of prostate, breast and colorectal cancer in farm residents compared to other rural and urban residents in New South Wales

This chapter is a manuscript that was prepared and submitted to *The Australian Journal of Rural Health* in December 2016 and is under review

Depczynski J, Dobbins T, Armstrong B, Lower T. **Stage of diagnosis of prostate, breast and colorectal cancer in farm residents compared to other rural and urban residents in New South Wales**
Manuscript prepared for peer review.

6.1 Abstract

Objective: To determine if stage at diagnosis of prostate, breast and colorectal cancers differs between farm, rural non-farm and urban residents. **Design:** Data-linkage of baseline survey information from a large cohort study, with state cancer registry records from 2006-2009. **Setting:** New South Wales (NSW), Australia. **Participants:** NSW residents enrolled in the 45 and Up Study cohort. **Main outcome measures:** Adjusted Odds Ratio of non-localised cancer stage was modelled using binary logistic regression, controlling for commonly known cancer risk factors. **Results:** Overall, differences in the odds ratios for later stage prostate, breast and colorectal cancer diagnosis in farm men and women compared to rural non-farm or urban counterparts, were not statistically significant; although farm men had twice the odds of either group of being diagnosed at later stage colorectal cancer. The odds of later stage prostate cancer for farm and urban men were similar, but rural non-farm men were significantly less likely than urban men to be diagnosed at later stage. Higher household income was associated with later stage breast and prostate cancer; and private health insurance with extras negatively associated with later stage prostate cancer. **Conclusions:** Differences in stage of cancer diagnosis, particularly between farm and rural non-farm men remain unexplained, but were not statistically significant. Farm men may be at higher risk of later stage colorectal cancer diagnosis, which if confirmed has implications for research on possible reasons; and for the delivery of appropriate cancer diagnostic services in rural areas.

Keywords: epidemiology, rural health services delivery, rural oncology, rural population health, research

6.2 Introduction

The most commonly diagnosed cancers in Australia are prostate, breast and colorectal cancers, which are also amongst the most highly amenable to screening and early diagnosis.¹ Earlier stage of diagnosis is a strong predictor of cancer survival, which has also been found to be poorer in rural areas.²⁻³ Reports on cancer in rural Australia seldom differentiate between farm and rural non-farm residents. However, recent analyses of the 45 and Up Study cohort, found little difference in prostate, breast or colorectal cancer incidence between farm and rural non-farm residents.⁴

International studies have generally reported reduced cancer risk in farmers compared to others for breast and colorectal cancers, with mixed results for prostate cancer.⁵⁻⁷ Stage at diagnosis has only been reported in two cohorts involving farmers in the international literature.^{6,8} This study will examine if stage at diagnosis differs between farm, rural non-farm and urban residents for prostate, breast and colorectal cancers. Findings may have implications for further research on health seeking behaviors; and the delivery of appropriate diagnostic services in rural areas.

6.3 Methods

This data linkage study was based on information from participants of the 45 and Up Study cohort, managed by the Sax Institute in collaboration with major Australian health agency partners. The cohort comprises 267,119 people aged 45 years and over, enrolled between January 2006 and December 2009. Details on the 45 and Up Study are available elsewhere.^{9 10}

The 45 and Up Study baseline questionnaire provided a range of information used to define the resident sub-groups; and on personal risk factors of participants. Records were linked with NSW Cancer Registry (NSW CR) data for February 2006 to December 2009. Cancer is a notifiable condition in NSW, with population-wide capture and information on stage collected. Further information on the NSW CR data collection and quality measures are published elsewhere.¹¹ Data linkage was

conducted by the NSW Centre for Health Record Linkage using probabilistic record linkage methods.¹² Logic checks were undertaken to check for data inconsistencies within and across datasets, with suspect records removed from analyses.

Participants with a cancer registration recorded in the NSW CR before the study recruitment date, or who had reported having ever been told by a doctor they had breast, prostate or other cancer (excluding skin cancer), were removed from analysis. This was to reduce the impact of changes in risk factors such as screening that may have arisen in response to a recent cancer diagnosis. However, sensitivity analyses comprised of all cases from 2006-2009, regardless of recruitment date.

6.3.1 Definition of variables

'Farm residents' were defined as those who indicated that they lived in a 'house on farm' on the 45 and Up Study baseline questionnaire. Rural 'non-farm' and urban residents were further defined using the Accessibility/Remoteness Index of Australia (ARIA+).¹³ Rural non-farm participants were those whose ARIA+ classification indicated they did not live in a 'Major city', excluding those who also specified that they lived in a 'house on farm.' Urban residents were those who lived in a 'Major city'. Where ARIA+ was not recorded, allocation was determined by cross-checking postcode of residence and distances to hospital services in data-linked hospital datasets.

The stage at diagnosis variable was taken from the 'degree of spread' variable defined in the NSW CR data dictionary.¹¹ Tumours localised to the tissue of origin (Stage 1 - 'early stage') were differentiated from those with regional spread to adjacent organs and/or regional lymph nodes, distant metastases or unknown sites (Stage 2 or above - 'later stage'). Risk factors considered for analysis were age at diagnosis, family history of cancer, private health insurance with extras status; and annual household income stratified by average annual household income in NSW in 2006.¹⁴ Commonly known modifiable risk factors for cancer were categorised to reflect national health or

workplace recommendations of the time.¹⁵⁻¹⁷ These were comprised of smoking as current, past, never; risky alcohol consumption of >5 days/week or >2 drink/day; overweight status (including obesity) with Body Mass Index>25; red meat consumption >3-4 serves/week; weekday sun exposure >1 hr/day<4 hr; and screening frequency <2 yrs, >2 yrs, unknown year or never.

6.3.2 Analytical procedures

Analyses were conducted using SAS 9.3™ software. Descriptive statistics were generated and binary logistic regression used to calculate adjusted odds ratios (OR) for later stage cancer diagnosis of breast, prostate and colorectal cancers, controlling for common cancer risk factors. As the primary target of interest, the farm resident group was used as the referent in the first instance. However, in order to compare odds ratios between rural non-farm and urban residents, secondary analyses were also undertaken using the urban group as the referent. Cases where stage was not recorded were excluded from analysis. Variables with univariate p values < .25 were included in the base model, with all possible interaction terms. Models were progressively reduced using a backward elimination approach, removing non-significant variables (at the .05 level), accounting for any non-significant confounders. Residual plots were examined to identify cases with undue influence in regression models.

6.4 Results

A total of 3270 persons from the 45 and Up Study cohort were diagnosed with either prostate, breast or colorectal cancer between recruitment and 31st December 2009. Proportions and odds ratios for later stage prostate, breast and colorectal cancers are shown for each resident group in Table 6.1. Variables in the final model were adjusted for all other remaining variables. Finally, additional odds ratios are provided for the rural non-farm group, compared to the urban group as referent.

Table 6.1: Non-localised stage of diagnosis for prostate, breast and colorectal cancers in farm, rural non-farm and urban residents, 2006-2009

Cancer Type (ICD9) ^a Total cancer cases where diagnosis after recruitment	Resident group	Total n	Cases diagnosed after recruitment & cancer stage known	Cases (%) of non-localised (Stage 2+) cancer	Adjusted odds ratio for non-localised cancer (95%CI)	Adjusted odds ratios (95% CI) for non-localised cancer in categories of variables remaining significant in final model
Prostate cancer (C61) Total n= 1,628 Stage known n= 1,005 (61.7%)	Farm	9,281	79	14 (17.7%)	1.00 (ref)	Annual household income over \$70,000 yes vs no OR= 1.74 (1.15 – 2.63)
	Rural non-farm	57,342	478	65 (13.6%)	0.64 (0.32 - 1.29)	Private insurance with extras yes vs no OR= 0.63 (0.43 – 0.93)
	Urban	57,286	448	82 (18.3%)	0.97 (0.49 - 1.93)	Significant difference rural non-farm vs. urban OR= 0.66 (0.45 – 0.98)
Breast (C50) (women) Total cases= 754 Stage known n= 726 (96.2%)	Farm	10,551	59	24 (40.7%)	1.00 (ref)	Annual household income over \$70,000 yes vs no OR= 1.51 (1.03 - 2.21)
	Rural non-farm	69,469	373	152 (40.8%)	1.11 (0.59 - 2.06)	
	Urban	63,190	294	129 (43.9%)	1.17 (0.62 - 2.22)	
Colorectal (C18-C21) (men) Total n= 502 Stage known n= 461 (91.8%)	Farm	9,281	28	20 (71.4%)	1.00 (ref)	No other significant factors
	Rural non-farm	57,342	219	116 (53.0)	0.45 (0.19 - 1.07)	
	Urban	57,286	214	118 (55.1%)	0.49 (0.21 - 1.17)	
Colorectal (C18-C21) (women) Total cases= 386 Stage known n= 350 (90.7%)	Farm	10,551	21	13 (61.9%)	1.00 (ref)	No other significant factors
	Rural non-farm	69,469	169	112 (66.3%)	1.21 (0.47 - 3.09)	
	Urban	63,190	160	96 (60.0%)	0.92 (0.36 - 2.35)	

Cancer stage was known for almost two-thirds of prostate cancer cases. After controlling for household income and private health insurance with extras status, there was little difference in the adjusted odds of later stage prostate cancer between farm and urban men. However, the adjusted odds for rural non-farm men was two-thirds that of farm men (OR 0.64, 95%CI 0.32 – 1.29) and urban men (OR 0.66, 95%CI 0.45 - 0.98). Stage was recorded for over 90% of colorectal cancer cases in men. Although not statistically significant, the proportion of farm men diagnosed at later stage was 16-18% higher than that of other men. Farm men also had twice the odds of being diagnosed at later stage of colorectal cancer than rural non-farm (OR=2.22, 95% CI 0.93-5.26) and urban men (OR=2.04, 95% CI 0.85-4.76), when the latter groups are used as referents.

For women, cancer stage was recorded for over 90% of breast and colorectal cases. Farm women were least likely to be diagnosed with later stage breast cancer adjusted for household income, although differences between groups were small. For colorectal cancer, farm women were somewhat less likely than rural non-farm women and more likely than urban women to be diagnosed at later stage. Again, differences between groups were not significant.

Higher household income was associated with later prostate and breast cancer stage; and private health insurance with extras negatively associated with later stage prostate cancer. No risk factors remained in adjusted models for colorectal cancer stage in either men or women. Results of sensitivity analyses were generally consistent with main findings for colorectal cancer, although confounders remained in prostate and breast cancer models.

6.5 Discussion

Proportions and odds of later stage prostate, breast or colorectal cancer in farm residents, were not significantly different from those of rural non-farm or urban residents. Farm men however, had twice the odds of the other groups of being diagnosed with later stage colorectal cancer. In contrast,

rural non-farm men were only two-thirds as likely as other groups to be diagnosed at later stage prostate cancer; significantly less so than urban men. These findings were not explained by the risk factors considered in the models. Household income was a significant positive correlate of late stage prostate cancer and breast cancer. Conversely, private health insurance with extras illustrated a significant negative correlation with advanced prostate cancer.

No other studies have compared cancer stage using these three sub-groups in the literature, although two-group comparisons have been made between 'farmers vs. others' and 'rural vs. urban' groups. Since farm residents in the Australian literature have not previously been differentiated from the larger 'rural' group of which they form part, comparisons with urban groups will not be exactly the same. However, some studies have reported later stage prostate and colorectal cancer diagnosis in rural Australians, compared to urban counterparts.¹⁸⁻¹⁹ This contrasts with our findings for prostate cancer, but is supportive of findings for colorectal cancer in farm versus urban men. Similar to our findings for breast cancer, no significant differences in stage were found between rural and urban women in a South Australian study.²⁰

There is only limited information in the literature elsewhere specific to stage of cancer diagnosis in farm residents. Compared to population counterparts, risk of later stage prostate, breast or colorectal cancer diagnosis was not found in Californian Hispanic farm-workers; nor for colorectal cancer stage in French farm men and women.^{6, 8} Findings in our study were similar to these cohorts for women, although slightly different for men. However, compared to our study, the French and Californian cohorts were younger and defined by occupation not residence.

Socio-economic disparities have been reported to affect stage of cancer diagnosis and it has been suggested rural location may multiply economic difficulties related to accessing distant health services.^{3 19} Later stage diagnosis for some cancers has been associated with greater distance from specialist diagnostic and treatment centres. This may relate to lag times between screening or initial

symptoms and definitive diagnosis. It is possible this contributes to later stage colorectal cancer diagnosis in farm men, but does not really explain why patterns of risk were different between farm and rural non-farm men, for colorectal and prostate cancer. Of note, higher household income was significantly associated with later stage prostate and breast cancer, which tends to contradict the socio-economic disparity argument. Whilst not always the case, lower levels of cancer screening have also been reported in rural Australia.²¹ However, these factors were accounted for in the modelling process, so do not explain remaining differences between groups.

There was little difference in screening practices between farm and rural non-farm residents found in the larger 45 and Up cohort, suggesting population-based screening does not explain the differences in stage of presentation between farm and rural non-farm men observed here. However, farm men were significantly less likely to visit a GP, which may have impacted upon prompt access and referral to specialist colonoscopy services.²² Since the majority of farms in Australia are small family owned businesses,²³ farm-related responsibilities and commitments may make it more difficult for farm residents to take time off to attend specialist appointments or access cancer treatment facilities. However, there was no documented evidence of this found in the literature. Further research on health seeking behaviours and diagnostic services in rural areas, may help to explain apparent differences in colorectal cancer stage between farm and rural non-farm men.

Another possible factor contributing to later stage colorectal cancer diagnosis in farm men is environmental exposure that may lead to more rapid disease progression. One study has examined associations between farm pesticide exposure and cancer stage, finding an association with later stage prostate cancer.²⁴ In contrast, farm men in our study had a similar prostate cancer stage profile to urban men, so observed patterns remain largely unexplained.

Limitations in this study include the short period of follow-up and relatively small farm case numbers that will have affected the width of confidence intervals for some analyses and potentially masked the significance of findings. However, since most differences did not reach statistical significance, discussion should be considered exploratory. Secondly, one-third of prostate cancer cases were of unknown stage, although this proportion was similar across groups. Reasons for the comparatively high proportion of unknown prostate cancer stage in the NSW CR data collection have been described elsewhere and our findings on this are consistent with others.²⁵ This reduces the case numbers available for analysis and the level of confidence that the proportion of later stage cancer correctly reflects that for all prostate cancer cases.

Thirdly, whilst a large and robust study with little evidence of risk factor bias, the 45 and Up Study cohort is not necessarily representative of the population of NSW aged 45 and over.⁹ However, this is unlikely to affect associations between Study variables and disease outcomes, as only internal comparisons were made.²⁶ Lastly, the definition of a 'farm resident' in this study was open to respondents' interpretation of a 'farm' and could include small holdings used for commercial, recreational or both purposes. Farm residents are a heterogeneous group and whilst small farm holdings make up the majority of farming enterprises in Australia, farm exposures could vary according to remoteness, primary production type or the proportion of activity deemed commercial.²³ The wide scope of farming and lack of clear definition around what constitutes a farm resident, has potentially led to an underestimation of any relationship between farm residence and cancer stage. Addressing difficulties in differentiating farm residents from others in administrative health datasets, may improve the precision of comparisons made in future studies.

6.6 Conclusion

Overall, differences in the likelihood of later stage prostate, breast and colorectal cancer diagnosis in farm men and women compared to rural non-farm and urban counterparts, were not

statistically significant. However, whilst the odds of later stage prostate cancer for farm and urban men was similar, rural non-farm men were significantly less likely than urban men to be diagnosed at later stage. In contrast, and whilst not significant, farm men had twice the odds of either group of being diagnosed at later stage colorectal cancer. Higher household income was positively associated with later stage prostate and breast cancer; and private health insurance with extras negatively associated with prostate cancer. However, patterns of risk between farm and rural non-farm men remain largely unexplained. Further research over a longer follow-up period or larger cohort is needed to confirm findings. An exploration of possible differences in health seeking behaviours and farm exposures is also warranted; which may have implications for screening programs and the delivery of earlier, more appropriate diagnostic services in rural areas.

6.7 Acknowledgments

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6.8 Appendix

Table 6.2: Comparison of non-localised stage of diagnosis for prostate, breast and colorectal cancers in farm, rural non-farm and urban residents, when diagnosis after recruitment (main analyses) versus diagnosis 2006-2009 (sensitivity analyses)

Main analyses						Sensitivity analyses				
Cancer Type (ICD9) ^a	Resident group	Total n	Cases diagnosed after recruitment & no prior cancer (stage known)	Cases (%) non-localised cancer (Stage 2+)	Adjusted odds ratio for non-localised cancer (95%CI)	Adjusted odds ratios (95% CI) for non-localised cancer in categories of variables remaining significant in final model	Cases diagnosed 2006-2009 incl. self-reported prior cancer (stage known)	Cases (%) non-localised cancer (Stage 2+)	Adjusted odds ratio for non-localised cancer (95%CI)	Adjusted odds ratios (95% CI) for non-localised cancer in categories of variables remaining significant in final model
Prostate (C61)	Farm	9,281	79	14 (17.7%)	1.00 (ref)	- Annual household income over \$70,000 Yes vs. no OR=1.74 (1.15 – 2.63) - Private insurance with extras Yes vs. no OR=0.63 (0.43 – 0.93) - Rural non-farm vs. urban OR 0.66 (0.45 – 0.98)	167	30 (18.0%)	1.00 (ref)	- PSA screening frequency p=.04 (trend) but no categories significant compared to referent < 2yrs - Private insurance with extras yes vs no OR= 0.66 (0.51 – 0.86) (Alcohol consumption > 5days/wk yes vs no OR= 0.62 (0.42 – 0.94) confounded by cohort x alcohol interaction)
	Rural non-farm	57,342	478	65 (13.6%)	0.64 (0.32 – 1.29)		1,129	127 (11.3%)	0.89 (0.45 – 1.75)	
	Urban	57,286	448	82 (18.3%)	0.97 (0.49 – 1.93)		1,013	148 (14.6%)	1.45 (0.74 – 2.83)	
Breast (C50) (women)	Farm	10,551	59	24 (40.7%)	1.00 (ref)	Annual household income over \$70,000 Yes vs. no OR=1.51 (1.03 - 2.21)	112	47 (41.9%)	1.00 (ref)	- Age at diagnosis OR= 0.98 (0.97 – 0.99) - Last breast screening: < 2yrs OR= 1.00 ref > 2yrs OR= 1.61 (1.09 – 2.39) Unknown yr OR= 1.82 (0.80 – 4.15) Never OR= 1.58 (0.89 – 2.79) - Private insurance with extras yes vs no OR= 0.74 (0.58 – 0.93) (Household income over \$70,000 / year not significant but confounded by significant cohort x income interaction terms)
	Rural non-farm	69,469	373	152 (40.8%)	1.11 (0.59 – 2.06)		838	352 (42.0%)	1.61 (0.91 – 2.87)	
	Urban	63,190	294	129 (43.9%)	1.17 (0.62 – 2.22)		759	325 (42.8%)	1.88 (1.04 – 3.38)	

Colorectal (C18 - C21) (men)	Farm	9,281	28	20 (71.4%)	1.00 (ref)	• No other significant factors	112	36 (65.5%)	1.00 (ref)	• Last colorectal screening < 2yrs OR= 1.00 ref > 2yrs OR= 0.87 (0.55 – 1.38) Unknown yr OR= 3.15 (1.01 – 9.82) Never OR= 1.34 (1.03 – 1.86) • Private insurance with extras yes vs no OR=0.76 (0.58 – 0.99)
	Rural non-farm	57,342	219	116 (53.0)	0.45 (0.19 - 1.07)		352	255 (53.2%)	0.56 (0.31 – 1.01)	
	Urban	57,286	214	118 (55.1%)	0.49 (0.21 - 1.17)		325	235 (53.4%)	0.58 (0.32 – 1.06)	
Colorectal (C18 - C21) (women)	Farm	10,551	21	13 (61.9%)	1.00 (ref)	• No other significant factors	47	24 (51.1%)	1.00 (ref)	• Last colorectal screening: < 2yrs OR= 1.00 ref > 2yrs OR= 1.61 (1.09 – 2.39) Unknown yr OR= 1.82(0.80 – 4.15) Never OR= 1.58 (0.89 – 2.79)
	Rural non-farm	69,469	169	112 (66.3%)	1.21 (0.47 - 3.09)		374	222 (59.4%)	1.38 (0.75 – 2.54)	
	Urban	63,190	160	96 (60.0%)	0.92 (0.36 - 2.35)		337	205 (60.8%)	1.56 (0.84 - 2.89)	

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Chapter 7: Cancer screening practices in a cohort of Australian farm, rural non-farm and urban residents aged 45 years and over

This chapter is a manuscript that was prepared for submission to *BMC Public Health* in February 2017 and is awaiting review.

Depczynski J, Dobbins T, Armstrong B, Lower T. **Cancer screening practices in a cohort of Australian farm, rural non-farm and urban residents aged 45 years and over.** Manuscript prepared for review.

7.1 Abstract

Background: Screening for breast, prostate, colorectal and cervical cancers can lead to earlier diagnosis and more effective treatment, but it is not known if cancer screening practices of farm residents in Australia differ from their rural or urban counterparts. **Methods:** Self-reported screening for prostate, breast and colorectal cancer were compared for farm, rural non-farm and urban participants of the 45 and Up Study cohort in New South Wales (NSW). Data for participants under 75 years of age and without prior cancer, were linked with NSW Pap Test Register records for cervical screening frequency from 2006-2012. Records were also linked with Medicare Benefits Schedule claims data for 2004-2011, for visits to a General medical Practitioner (GP); and for breast, prostate and colorectal screening procedures. Age-adjusted comparisons were made using general linear regression and logistic regression. **Results:** Farm residents were significantly less likely to visit a GP, but screening practices between farm and rural non-farm residents were generally similar. Urban residents had significantly more prostate specific antigen (PSA) tests, Pap tests, mammograms and colonoscopies than either of the other groups. Urban residents were also significantly more likely to report ever having a mammogram or colonoscopy. In contrast, farm and rural non-farm residents had significantly more Faecal Occult Blood Tests (FOBTs) than urban counterparts; and were around one third more likely than urban residents to report ever having a FOBT. Farm residents were most likely to report ever having a PSA test or 'any' form of colorectal screening test; with both rural groups significantly more likely to do so than urban residents. **Conclusions:** Farm and rural non-farm residents had lower utilisation and perhaps reduced access to specialist or procedural screening services.

Keywords: Farm*, cancer, screening, rural, prostate, breast, colorectal, bowel

7.2 Introduction

Better outcomes for some of the most common cancers, breast, prostate, colorectal and cervical cancers, can be achieved by use of screening tests in defined, at risk groups. Screening aims to identify early signs of cancer before symptoms emerge; and can lead to effective early treatment and significant reductions in progression to metastases or mortality.¹⁻⁷ Cancer screening in Australia is conducted through age and sex specific population-based programs, as well as through individual consultation with medical and allied health practitioners.^{1,8}

It has been suggested that higher mortality and incidence of some cancers in rural areas, may be due to reduced access to health services, perhaps because of lack of screening or delayed diagnosis of symptomatic cancers, although the evidence for this is mixed.⁹⁻¹⁵ Information on health service utilisation by farm residents is scant, because standard health reports do not distinguish between this group and other rural people. This study explores differences in cancer screening and utilisation of General medical Practitioners (GPs) by farm, rural non-farm and urban residents of the 45 and Up Study cohort, in New South Wales (NSW), Australia. Findings may assist those conducting rural cancer screening programs or aiming to achieve earlier diagnosis of symptomatic cancers in rural residents.

7.3 Methods

Information from the 45 and Up Study baseline questionnaire was linked with data from two administrative health datasets. The 45 and Up Study is managed by the Sax Institute, in collaboration with major health agency partners. It comprises of 267,119 NSW residents aged 45 years or over who enrolled in the Study between January 2006 and December 2009. Eligible individuals were randomly sampled from the enrolment database of the Australian Department of Human Services (formerly Medicare Australia), which provides near complete coverage of the NSW population. Details of the 45 and Up Study cohort, sampling, recruitment, variable definitions and data quality measures are available elsewhere.¹⁶⁻¹⁸

Baseline questionnaire information was used to define participants as farm, rural non-farm and urban groups; and to obtain self-report information on prostate, breast and colorectal cancer screening practices. Linkage of the 45 and Up Study cohort data to Medicare Benefits Schedule (MBS) claims data for 2004-2011, was done by the Sax Institute using a unique identifier that was provided to the Australian Department of Human Services (DHS). The MBS is a national database of all medical and allied health consultations and procedures provided by registered health professionals and subsidised by the Australian Government. Participant records were also linked with data in the NSW Pap Test Register for 2006 - 2012, by the NSW Centre for Health Record Linkage, using probabilistic linkage methods.¹⁹ Data logic checks were undertaken to check for inconsistencies within and across datasets, with suspect records removed from analyses.

Records of participants with prior diagnosis of cancer were removed from analysis and only participants 45 to 75 years of age were included in the primary analysis, as this is the age group in which most cancer screening is recommended.²⁰⁻²² Sensitivity analyses included all ages.

‘Farm residents’ were defined as those who indicated in the 45 and Up Study baseline questionnaire that they lived in a ‘house on farm’. Rural ‘non-farm’ and urban residents were further defined using the Accessibility/Remoteness Index of Australia (ARIA+) from postcode of residence at recruitment.²³ Those participants who did not live in a house on a farm whose ARIA+ classification indicated they did not live in a ‘Major city’, were defined as rural non-farm residents. Those whose ARIA+ classification indicated they lived in a ‘Major city’ were urban residents. Where ARIA+ was not recorded, allocation was determined by cross-checking with postcode of residence and distances to treating hospitals in linked hospital datasets.

Participants reported whether they had ever had a Prostate Specific Antigen test (PSA test) for prostate screening; or a mammogram for breast screening. For colorectal cancer, participants were asked whether they had ever had a Faecal Occult Blood Test (FOBT), colonoscopy or sigmoidoscopy. Participants

who reported screening were further asked when their last screening test was conducted, which was categorised as within the past 2 years, more than 2 years ago, in an unknown year or never.

Cervical screening frequency was determined using the number of Pap tests registered in the NSW Pap Test Register from 2006-2012 for each woman. Average frequency of visits to a GP were determined using total visits per person for 2004-2011 as identified by 2011 MBS item description codes (2-52, 192-200, 597, 599, 2496-2560, 4999-5068).²⁴ Average frequency of screening tests over the period were determined in the MBS for PSA tests (MBS code 66655), bilateral mammograms (59300-59301), colonoscopies (32090) and FOBTs (66764). Mammograms claimed through the MBS are primarily undertaken for diagnostic purposes, but claims for bilateral mammograms are known to sometimes be screening mammograms.

Analysis was conducted using SAS 9.3™²⁵. General linear regression modelling was used to calculate mean number of GP visits, PSA tests, mammograms, colonoscopies, FOBT's and Pap tests in the periods studied for each residence group, adjusted for age. Binary logistic regression was used to assess the odds of ever having screened for prostate, breast and colorectal cancer (any, FOBT, colonoscopy); and the odds for having screened in the 'last 2 years' out of those who screened.

7.4 Results

Farm men and women in the cohort were 3 to 4 years younger than rural non-farm and urban counterparts. Those aged under 75 years comprised approximately 80% of the cohort. Table 1 and Table 2 show for each gender, the average age-adjusted GP visits (per year), PSA tests, bilateral mammograms, colonoscopies, FOBT's and Pap-tests per person; as well as the proportions and age-adjusted odds ratios for self-reported 'ever' and 'last' prostate, breast and colorectal screening.

Table 7.1: Visits to General medical Practitioners (GP) and cancer screening practices of farm, rural non-farm and urban men 45-74 years

Characteristic or cancer - related health activity	Total n	Farm	Rural	Urban
Average age of participants in years, excl. prior cancer cases (95%CI)	101,577	61.5 (61.2 – 61.7)	63.8 (63.7 – 63.9)	64.2 (64.1 – 64.3)
Number of participants aged less than 75 yrs (%)	84,174	7,168 (91.2%)	39,242 (84.2%)	37,764 (80.2%)
1. Visits to General Practitioners (GPs) on MBS (Jan 2004 - Dec 2011)¹				
Average GP visits /yr (age-adjusted)	74,949	0.79 (0.76 – 0.81)	0.82 (0.81 – 0.83)	0.87 (0.86 – 0.88)
2. Prostate cancer screening				
PSA Tests in MBS (Jan 2004 - Dec 2011)¹				
% men less than 75 yrs of age who had at least one test	78,813	5,094 (74.6%)	27,151 (74.6%)	26,454 (74.4%)
Average no. PSA tests / person (age-adjusted)	78,813	1.43 (1.41 – 1.46)	1.45 (1.43 – 1.46)	1.48 (1.46 – 1.49)
Self-reported prostate cancer screening in men < 75yrs²				
Ever had a PSA test (yes n %)	83,674	4,931 (69.5%)	27,593 (70.6%)	25,265 (67.4%)
Age-adjusted OR (yes)	83,672	1.00	0.99 (0.93 – 1.05)	0.91 (0.86 – 0.96)
Rural non-farm vs urban OR=1.09 (1.05 – 1.12)]				
Frequency of screening ³ : last test < 2 years ago (n %)	83,176	4,067 (57.6%)	22,847 (58.8%)	20,973 (56.3%)
Age-adjusted OR: last test < 2 years ago of those who screened	57,291	1.00	0.99 (0.91 – 1.08)	0.97 (0.89 – 1.05)
Rural non-farm vs urban OR=1.02 (0.98 – 1.07)				
3. Colorectal cancer screening				
Screening tests recorded in MBS (Jan 2004 - Dec 2011)¹				

FOBT's				
% men less than 75 yrs of age who had at least one FOBT	79,402	246 (3.6%)	1,201 (3.3%)	952 (2.7%)
Average no. FOBT tests / person (age-adjusted)	78,813	0.06 (0.05 – 0.06)	0.05 (0.05 – 0.05)	0.04 (0.04 – 0.04)
Colonoscopies				
% men <75 yrs who had at least one colonoscopy	79,402	1,044 (15.2%)	5,574 (15.2%)	7,348 (20.5%)
Average no. colonoscopies / person (age-adjusted)	78,813	0.19 (0.17 – 0.20)	0.19 (0.18 – 0.19)	0.26 (0.25 – 0.26)
Self reported colorectal cancer screening in men < 75yrs²				
Ever had any bowel cancer screening test ⁴ (yes n %)	83,799	3,713 (52.2%)	20,548 (52.5%)	18,135 (48.3%)
Age-adjusted OR (yes)	83,797	1.00	0.96 (0.91 – 1.01)	0.85 (0.81 – 0.90)
Rural non-farm vs urban OR=1.13 (1.10 – 1.16)				
Ever had a FOBT test (yes n %)	85,537	2,211 (30.5%)	12,657 (31.7%)	9,653 (25.2%)
Age-adjusted OR (yes)	85,535	1.00	1.02 (0.96 – 1.08)	0.76 (0.72 – 0.81)
Rural non-farm vs urban OR=1.34 (1.29 – 1.38)				
Ever had a colonoscopy (yes n %)	85,536	2,078 (28.7%)	11,640 (29.2%)	11,400 (29.7%)
Age-adjusted OR (yes)	85,534	1.00	0.99 (0.93 – 1.04)	1.05 (1.00 – 1.11)
Rural non-farm vs urban OR=0.93 (0.91 – 0.96)				
Frequency of screening ³ : last test < 2 years ago (n %)	83,412	2,440 (34.5%)	13,684 (35.1%)	11,981 (32.0%)
Age-adjusted OR: last test < 2 years ago of those who screened	42060	1.00	0.97 (0.90 – 1.04)	0.99 (0.92 – 1.07)
Rural non-farm vs urban OR=0.98 (0.94 – 1.02)				

1. Claims made by health service providers for items on government subsidised Medicare Benefits Schedule (MBS), 2004-2011, excluding prior cancer cases
2. Self reported responses to 45 and Up Study baseline questionnaire, excluding prior cancer cases
3. Where frequency reported
4. FOBT, colonoscopy or sigmoidoscopy

Table 7.2: Visits to General medical Practitioners (GP) and cancer screening practices of farm, rural non-farm and urban women 45-74 years

Characteristic or cancer - related health activity	Total n	Farm	Rural	Urban
Average age of participants in years, excl. prior cancer cases (95%CI)	121,136	59.2 (59.0 – 59.4)	62.4 (62.3 – 62.5)	63.0 (62.8 – 63.1)
Number of participants aged less than 75 yrs (%)	103,165	8,636 (94.5%)	50,535 (86.5%)	43,994 (82.2%)
1. Visits to General Practitioners (GPs) in MBS (Jan 2004 - Dec 2011) ¹				
Average GP visits /yr (age-adjusted)	94,218	0.67 (0.65 – 0.69)	0.73 (0.72 – 0.74)	0.80 (0.79 – 0.81)
2. Breast cancer screening				
Mammograms recorded in MBS (Jan 2004 - Dec 2011) ¹²				
% women who had at least one mammogram	98,469	1,782 (21.2%)	10,029 (20.9%)	10,127 (24.0%)
Average no. mammograms / person (age-adjusted)	97,775	0.40 (0.37 – 0.42)	0.39 (0.38 – 0.40)	0.49 (0.48 – 0.50)
Self-reported breast cancer screening ³				
Ever had a mammogram (yes n %)	102,434	7,557 (88.4%)	44,892 (89.3%)	38,986 (89.4%)
Age-adjusted OR	102,425	1.00	0.99 (0.92 – 1.06)	1.09 (1.01 – 1.17)
			Rural non-farm vs urban OR=0.91 (0.87 – 0.95)]	
Frequency of screening ⁴ : last test < 2 years ago (n %)	101,568	6,111 (72.0%)	36,180 (72.6%)	31,459 (72.8%)
Age-adjusted OR: last test < 2 years ago of those who screened	90,572	1.00	1.04 (0.97 – 1.11)	1.02 (0.95 – 1.08)
			Rural non-farm vs urban OR=1.02 (0.99 – 1.06)	
3. Colorectal screening				
Screening tests recorded in MBS (Jan 2004 - Dec 2011) ¹				

FOBT's				
% women <75yrs who had at least one FOBT	98,469	260 (3.1%)	1,421 (3.0%)	935 (2.2%)
Average no. FOBTs / person (age-adjusted)	97,775	0.04 (0.04 – 0.05)	0.04 (0.04 – 0.04)	0.03 (0.03 – 0.03)
Colonoscopies				
% women<75yrs who had at least one colonoscopy	98,469	1,448 (17.3%)	8,471 (17.7%)	9,757 (23.2%)
Average no. colonoscopies / person (age-adjusted)	97,775	0.22 (0.20 – 0.23)	0.21 (0.21 - 0.22)	0.29 (0.28 – 0.29)
Self reported colorectal screening³				
Ever had any bowel screening test ⁵ (yes n %)	102,036	3,900 (45.7%)	23,427 (46.8%)	19,098 (44.0%)
Age-adjusted OR	102,027	1.00	0.97 (0.93 – 1.12)	0.90 (0.86 – 0.95)
Rural non-farm vs urban OR=1.07 (1.05 – 1.10)				
Ever had a FOBT test (yes n %)	104,508	2,168 (24.9%)	12,301 (24.0%)	8,787 (19.7%)
Age-adjusted OR	104,499	1.00	0.89 (0.85 – 0.94)	0.72 (0.68 – 0.76)
Rural non-farm vs urban OR=1.24 (1.20 – 1.28)				
Ever had a colonoscopy (yes n %)	104,506	2,399 (27.6%)	15,340 (29.9%)	13,285 (29.8%)
Age-adjusted OR	104,497	1.00	1.05 (1.00 – 1.11)	1.09 (1.04 – 1.15)
Rural non-farm vs urban OR=0.97 (0.94 – 0.99)				
Frequency of screening ⁴ : last test < 2 years ago (n %)	101,556	2,475 (29.1%)	14,922 (30.0%)	12,155 (28.1%)
Age-adjusted OR: last test < 2 years ago of those who screened	45,970	1.00	0.99 (0.92 – 1.06)	0.99 (0.92 – 1.07)
Rural non-farm vs urban OR=1.00 (0.96 – 1.04)				
4. Cervical screening⁶ - NSW Pap Test Register				
Jan 2006 – March 2013				
% aged <75 yrs who screened at least once	112,092	6,514 (68.9%)	35,096 (63.9%)	33,059 (69.3%)

Average Pap tests/person (age adjusted)	112,092	1.98 (1.94 – 2.00)	1.87 (1.86 – 1.89)	2.07 (2.05 – 2.09)
Average Pap tests/person excl. those who never screened (age-adjusted)	74,669	2.91 (2.87 – 2.94)	2.90 (2.89 – 2.91)	3.01 (3.00 – 3.02)

1. Claims made by health service providers for items on government subsidised Medicare Benefits Schedule (MBS), 2004-2011, excluding prior cancer cases
2. Participants screened through BreastScreen Australia do not appear as claims in MBS data
3. Self reported responses to 45 and Up Study baseline questionnaire, excluding prior cancer cases
4. Where frequency reported
5. FOBT, colonoscopy or sigmoidoscopy
6. Pap Test Register cervical screening data does not exclude those with a prior cancer

7.4.1 Visits to General Practitioners

On average farm men and women in the screening age group were less likely to visit a GP over the period than rural non-farm counterparts, with this difference being significant for women. Farm and rural non-farm men and women were significantly less likely than urban residents to visit a GP.

7.4.2 Cancer screening in men

Farm and rural non-farm men did not differ significantly from each other in the average number of PSA tests over the 2004-2011 period; or in the odds of ever having had a test for prostate cancer. Urban men had significantly more PSA tests per person than farm men, but the differences were small. In contrast, the odds of reporting ever having had a PSA test were 9% higher in farm and rural non-farm men than urban men. Whilst not significant, both groups also had higher odds than urban men of having had a screening test in the last 2 years.

For colorectal cancer, variations in screening test usage between farm and rural non-farm groups were also similar, but significantly different to urban men. The odds of having an FOBT for both groups was approximately one-third greater than for urban men. Farm men also had significantly greater odds of reporting ever having 'any' colorectal screening test than urban men; and were most likely to report being screened in the last 2 years, although differences in the latter were marginal. In contrast, urban men had significantly greater odds of having a colonoscopy.

7.4.3 Cancer screening in women

Similarly, farm and rural non-farm women did not differ significantly from each other in the average number, or odds of having had a mammogram. Urban women had significantly more mammograms recorded in the MBS data; as well as 9% greater odds of reporting ever having a mammogram, than the

other two groups. Rural non-farm women were most likely to report having had a mammogram in the last 2 years, although differences were not significant and relatively small.

There was little difference between farm and rural non-farm women in the number or odds of having an FOBT or colonoscopy. However, urban women had significantly fewer FOBT's than either of the other groups. Urban women also had significantly lower odds of reporting ever having had an FOBT, or to have had 'any' colorectal screening test in the past 2 years. Conversely, urban women had significantly more colonoscopies and greater odds of ever having had a colonoscopy than farm or rural non-farm counterparts. There was little difference between groups in self-reported frequency of having had a colorectal screening test.

Urban women had significantly more Pap tests than farm women, who in turn had significantly more tests than rural non-farm women. Excluding women who did not have any Pap tests, urban women still had more tests on average over the period, but differences between farm and rural non-farm women were no longer significant.

Results and screening patterns between groups in the sensitivity analyses that included all ages were similar to those of the primary analyses.

7.5 Discussion

Farm residents visited a GP the least often, but this may be of limited practical significance. Overall differences in screening between farm and rural non-farm residents were mostly non-significant, although screening patterns were sometimes different for urban residents. Trends across groups in MBS data did not always correspond with trends in the self-report data, such as for PSA tests. However, tests recorded in the MBS could have been for either diagnostic or screening purposes, so the use of different measures in each dataset may have contributed to some inconsistencies.

Urban residents had significantly more colonoscopies per person and greater odds of a colonoscopy, significantly so for men. Differences between farm and rural non-farm residents in utilisation of FOBTs and colonoscopies were marginal. Importantly, both groups had one-third greater odds of having an FOBT than urban counterparts; and were more likely to report having had 'any' colorectal screening test. Urban women had significantly more Pap tests than farm and rural non-farm women. Results of sensitivity analyses were generally consistent with main findings.

There are three population-based screening programs currently in operation in Australia; BreastScreen Australia, the National Cervical Screening Program, and the National Bowel Cancer Screening Program.^{1, 8} Breast and colorectal screening, along with PSA testing, may also be conducted by private practitioners, based on individual risk factors.²⁶ However, although asymptomatic individuals in target age-groups are encouraged to screen, similar tests are conducted on people displaying symptoms. Therefore, it cannot be claimed that all mammograms, PSA tests, FOBTs or colonoscopies in the MBS were for screening purposes - nor how the term 'screening' is understood when participants self-report their testing. Misclassification is most likely to have occurred in the direction of 'screening', when asymptomatic screening by public health definitions, did not actually occur. This may have led to an overestimate of screening rates per se, although this is likely to have affected residence groups equally. Removing prior cancer cases and those over 75 years attempted to minimise misclassification errors.

7.5.1 General Practitioners

In Australia, GP's are usually the first point of contact for healthcare including arrangement of tests for both diagnostic and screening purposes.²⁷ National health expenditure data on GP services, pathology, imaging and specialist services demonstrates an age-standardised decrease in expenditure per person, with increasing remoteness from urban centres.¹⁴ However, little difference between rural and urban residents was found in a self-report study of GP attendance in South Australia.¹⁵

Only two reports have been reported on utilisation of GP services by Australian farm residents. No significant differences in GP attendance were noted between farmers and comparison groups in rural NSW and Queensland.²⁸⁻²⁹ One US study likewise found little difference between farmers and others in GP attendance³⁰; although another found that farm men were less likely to have had a primary care check-up in the past year than non-farm men.³¹ Most of these studies, however, were of cross-sectional design and comprised less than 1000 farm residents. In contrast, our study was more substantial in size and able to retrieve data on consultations over an 8 year period. Nevertheless, people may visit a GP attendance for a variety of reasons other than screening – so there may be many reasons why farm residents might be less likely to attend a GP. These may include reduced access to or supply of GP services, or alternatives offered by hospital-based health services;^{14, 32} although such issues are likely to affect rural non-farm residents in a similar way. Alternatively, farm residents may enjoy a healthier state of well-being, reflecting a healthy worker effect or a more outdoor, physically active lifestyle, as suggested elsewhere.³³ Further discussion of these factors lies outside the scope of the data and this discussion.

7.5.2 Screening

Some Australian studies have reported lower cancer screening rates in rural compared to urban areas,⁹⁻¹⁰ whilst others have reported little difference.¹¹⁻¹³ Participation rates in population-based breast, cervical and colorectal cancer screening programs, have generally been higher in regional rather than urban areas, although lowest in very remote areas.²⁰⁻²²

The low proportion of mammograms in the MBS compared to self-report data, is likely a reflection of the extensive role of BreastScreen Australia in providing population-based screening, which are not included in MBS claims data. By either measure, urban women underwent more breast screening, but differences between groups remained relatively small and we cannot discount that participants were also reporting on diagnostic mammograms. Greater use of mammograms amongst urban women in the MBS may also reflect greater availability and use of private diagnostic services in urban areas.

MBS data indicated that urban residents were also significantly more likely to have had a colonoscopy. As for mammograms, it is not known what proportion of colonoscopies in the MBS data are for diagnostic purposes, which is an inherent difficulty with administrative health datasets described by others.³⁴⁻³⁶ One study using patient perceptions and another using medical records, both found that around one third of colonoscopies were for screening purposes; a further third for surveillance and the remainder for diagnostic and related purposes.^{34, 37} Another study reported that up to a half of endoscopies were for screening.³⁸ Our study removed prior cancer cases so the proportion for surveillance purposes is likely to be reduced.

Self-reported use of colonoscopy for screening purposes, has previously been shown to be reasonably accurate.^{34, 39} In addition, colonoscopies recorded in Australian administrative datasets have also been shown to be quite accurate.⁴⁰ By both MBS and self-report measures in our study, there was a consistent trend for greater use of colonoscopies by urban residents. This may partly reflect greater availability of colonoscopy services in urban areas as an alternative to FOBT as a screening tool; which has the time saving potential to remove suspect lesions during the procedure. In contrast and perhaps reflecting lower availability of colonoscopy services, FOBTs were significantly more likely to have been used in farm and rural non-farm and farm residents than urban counterparts. This is consistent with results for participation by rurality in the National Bowel Cancer Screening Program, which uses the FOBT as the screening tool.²¹

Six studies were identified in the international literature that compared screening practices between farm and non-farm comparison groups. The only study reporting on prostate cancer screening, found that farm residents in Iowa were less likely to have had a prostate examination than rural non-farm counterparts.³¹ For colorectal cancer, there were no significant differences between farm and rural non-farm residents in the same cohort; although another study found farmers were less likely to have an FOBT in the past year than other workers.³⁰

Most studies of breast cancer screening have reported similar practices between farm and non-farm groups;^{30, 41-43} or if lower in farmers, this was related more to age, education and health insurance factors than farm residence itself.^{31, 42} For cervical screening, two studies reported similar practices between farm and other women;³⁰⁻³¹ whilst two others found farm women less likely to have had cervical screening than other rural women.^{41, 44} It was proposed that social isolation of farm women rather than geographic distance to services, may have contributed to the latter. Overall, whilst reports in the international literature were few and results mixed, there was little evidence that cancer screening practices between farm residents and others differed to any great extent. These conclusions are generally consistent with the findings of our study, especially regarding the relatively small differences between farm and rural non-farm residents.

7.5.3 Limitations

Results need to be considered in light of the interpretation of self-report and MBS data for different cancers already discussed. It should also be noted that the 45 and Up Study cohort is not strictly representative of the corresponding population of NSW, although linkage with population datasets has shown that biases are limited.^{16, 45} The definition of a 'farm resident' in this study was also open to respondents' interpretation of a 'farm' and could include small holdings used for commercial, recreational or both purposes. As such, exposures, practices and lifestyles of farm residents could vary accordingly, with differences between residents in these respects not always clearly defined.⁴⁶ This may have affected representativeness of sub-groups and internal validity of comparisons made. However, errors arising from misclassification of resident group are likely to be non-differential and independent of other risk factors, leading to a null bias and underestimation of relationships between farm residence and cancer screening.

7.6 Conclusions

Farm residents were significantly less likely to visit a GP, but screening practices between farm and rural non-farm residents were generally similar. As a group, urban residents had significantly more PSA

tests and procedural screening tests such as mammograms, colonoscopies and Pap tests. In contrast, rural non-farm and farm residents were significantly more likely than urban residents to self-report having a PSA test or FOBT; and had significantly more FOBT's claimed through the MBS than their urban counterparts. This suggests farm and rural non-farm residents may have had reduced preference, access or opportunity for cancer screening that required specialist services.

7.7 Acknowledgements

The *45 and Up Study* is managed by the Sax Institute in collaboration with major partner Cancer Council NSW; and partners: the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; NSW Government Family & Community Services - Ageing, Carers and the Disability Council NSW; and the Australian Red Cross Blood Service. We would like to thank the many thousands of people participating in the 45 and Up Study.

The Australian Department of Human Services is also acknowledged for its role in provision of the MBS data and unique identifiers that enabled linkage of the data

7.8 Appendix

Table 7.3: Visits to General medical Practitioners (GP) and cancer screening practices of farm, rural non-farm and urban men 45-74 years (main analyses), compared to all men aged 45 years and over (sensitivity analyses)

Characteristic or cancer - related health activity	Age <75 years and excluding prior cancer				All men 45 years and over			
	Total n	Farm	Rural	Urban	Total n	Farm	Rural	Urban
1. Visits to General Practitioners (GPs) on MBS (Jan 2004 - Dec 2011) ¹								
Average GP visits /yr (age-adjusted)	74,949	0.79 (0.76 – 0.81)	0.82 (0.81 – 0.83)	0.87 (0.86 – 0.88)	123,148*	1.18 (1.15 – 1.21)	1.24 (1.23 – 1.25)	1.30 (1.29 – 1.31)
2. Prostate cancer screening								
PSA Tests in MBS (Jan 2004 - Dec 2011) ¹								
% men who had at least one test	78,813	74.6%	74.6%	74.4%	123,909*	73.5%	72.3%	71.0%
Average no. PSA tests / person (age-adjusted)	78,813	1.43 (1.41 – 1.46)	1.45 (1.43 – 1.46)	1.48 (1.46 – 1.49)	123,148*	1.45 (1.42 – 1.47)	1.43 (1.42 – 1.44)	1.40 (1.39 – 1.41)
Self-reported prostate cancer screening in men²								
Ever had a PSA test (yes %)	83,674	69.5%	70.6%	67.4%	98,850	69.7%	71.2%	68.6%
Age-adjusted OR (yes)	83,672	1.00	0.99 (0.93 – 1.05)	0.91 (0.86 – 0.96)	98,848	1.00	0.99 (0.94 – 1.05)	0.86 (0.82 – 0.91)
Frequency of screening: last test < 2 years ago (%)	83,176	57.6%	58.8%	56.3%	98,904	57.3%	58.2%	55.6%
Age-adjusted OR: last test < 2 years ago of those who screened	57,291	1.00	0.99 (0.91 – 1.08)	0.97 (0.89 – 1.05)	68,308	1.00	0.99 (0.94 – 1.04)	0.88 (0.84 – 0.93)
3. Colorectal cancer screening								
Screening tests recorded in MBS (Jan 2004 - Dec 2011) ¹								
FOBT's								
% men who had at least one FOBT	79,402	3.6%	3.3%	2.7%	123,909*	16.2%	19.0%	13.4%
Average no. FOBT tests / person (age-adjusted)	78,813	0.06 (0.05 – 0.06)	0.05 (0.05 – 0.05)	0.04 (0.04 – 0.04)	123,148*	0.25 (0.23 – 0.26)	0.29 (0.28 – 0.29)	0.19 (0.18 – 0.20)

Colonoscopies								
% men who had at least one colonoscopy	79,402	15.2%	15.2%	20.5%	123,909*	23.8%	23.5%	30.1%
Average no. colonoscopies / person (age-adjusted)	78,813	0.19 (0.17 – 0.20)	0.19 (0.18 – 0.19)	0.26 (0.25 – 0.26)	123,148*	0.38 (0.36 – 0.39)	0.36 (0.35 – 0.37)	0.47 (0.46 – 0.47)
Self reported colorectal cancer screening in men²								
Ever had any bowel cancer screening test ⁴ (yes %)	83,799	52.2%	52.5%	48.3%	99,109	52.4%	53.0%	48.9%
Age-adjusted OR (yes)	83,797	1.00	0.96 (0.91 – 1.01)	0.85 (0.81 – 0.90)	99,107	1.00	0.97 (0.92 – 1.01)	0.81 (0.77 – 0.85)
Frequency of screening: last test < 2 years ago (%)	83,412	34.5%	35.1%	32.0%	98,533	33.9%	34.6%	31.3%
Age-adjusted OR: last test < 2 years ago , of those who screened	42,060	1.00	0.97 (0.90 – 1.04)	0.99 (0.92 – 1.07)	50,083	1.00	0.99 (0.95 – 1.05)	0.85 (0.81 – 0.90)

1 Claims made by health service providers for items on government subsidised Medicare Benefits Schedule (MBS), 2004-2011

2 Self reported responses to 45 and Up Study baseline questionnaire, excluding prior cancer cases

3 Where frequency reported

4 FOBT, colonoscopy or sigmoidoscopy

** Some data include cases of self reported prior cancer (1) Sensitivity analyses of MBS claims and (2) All analyses of NSW Pap Test Register data

Table 7.4: Visits to General medical Practitioners (GP) and cancer screening practices of farm, rural non-farm and urban women 45-74 years (main analyses), compared to all women aged 45 years and over (sensitivity analyses)

Characteristic or cancer - related health activity	Age <75 years and excluding prior cancer				All women 45 years and over (incl. prior cancer)			
	Total n	Farm	Rural	Urban	Total n	Farm	Rural	Urban
1. Visits to General Practitioners (GPs) on MBS (Jan 2004 - Dec 2011) ¹								
Average GP visits /yr (age-adjusted)	94,218	0.67 (0.65 – 0.69)	0.73 (0.72 – 0.74)	0.80 (0.79 – 0.81)	142,369*	0.89 (0.86 – 0.91)	0.94 (0.93 – 0.94)	1.02 (1.01 – 1.03)
2. Breast cancer screening								
Mammograms in MBS (Jan 2004 - Dec 2011) ¹								
% women who had at least one test	98,469	21.2%	20.9%	24.0%	143,210*	23.8%	23.3%	25.5%
Average no. mammograms/ person (age-adjusted)	97,775	0.40 (0.37 – 0.42)	0.39 (0.38 – 0.40)	0.49 (0.48 – 0.50)	142,369*	0.53 (0.51 – 0.56)	0.56 (0.55 – 0.57)	0.65 (0.64 – 0.67)
Self-reported breast cancer screening in women²								
Ever had a mammogram (yes %)	102,434	88.4%	89.3%	89.4%	118,502	88.2%	88.9%	88.6%
Age-adjusted OR (yes)	102,425	1.00	0.99 (0.92 – 1.06)	1.09 (1.01 – 1.17)	118,493	1.00	0.94 (0.88 – 1.01)	0.99 (0.92 – 1.06)
Frequency of screening: last test < 2 years ago (%)	101,568	72.0%	72.6%	72.8%	117,279	69.8%	66.8%	64.6%
Age-adjusted OR: last test < 2 years ago, of those who screened	90,572	1.00	1.04 (0.97 – 1.11)	1.02 (0.95 – 1.08)	93,889	1.00	0.96 (0.91 – 1.01)	0.87 (0.83 – 0.92)
3. Colorectal cancer screening								
Screening tests recorded in MBS (Jan 2004 - Dec 2011) ¹								
FOBT's								
% women who had at least one FOBT	98,469	3.1%)	3.0%	2.2%	143,210*	14.4%	16.8%	12.0%
Average no. FOBT tests / person (age-adjusted)	97,775	0.04 (0.04 – 0.05)	0.04 (0.04 – 0.04)	0.03 (0.03 – 0.03)	142,369*	0.20 (0.19 – 0.22)	0.24 (0.23 – 0.24)	0.16 (0.16 – 0.17)

Colonoscopies								
% women who had at least one colonoscopy	98,469	17.3%	17.7%	23.2%	143,210*	22.2%	22.6%	29.0%
Average no. colonoscopies / person (age-adjusted)	97,775	0.22 (0.20 – 0.23)	0.21 (0.21 - 0.22)	0.29 (0.28 – 0.29)	142,369*	0.32 (0.30 – 0.33)	0.32 (0.32 – 0.33)	0.42 (0.42 – 0.42)
Self reported colorectal cancer screening in women²								
Ever had any bowel cancer screening test ⁴ (yes %)	102,036	45.7%	46.8%	44.0%	117,891	45.6%	47.2%	44.7%
Age-adjusted OR (yes)	102,027	1.00	0.97 (0.93 – 1.12)	0.90 (0.86 – 0.95)	117,882	1.00	0.98 (0.94 – 1.03)	0.87 (0.83 – 0.91)
Frequency of screening: last test < 2 years ago (%)	101,556	29.1%	30.0%	28.1%	117,187	28.7%	29.2%	27.0%
Age-adjusted OR: last test < 2 years ago of those who screened	45,970	1.00	0.99 (0.92 – 1.06)	0.99 (0.92 – 1.07)	53,507	1.00	0.99 (0.95 – 1.05)	0.89 (0.84 – 0.93)
4. Cervical screening⁶ - NSW Pap Test Register** Jan 2006 – March 2013								
% who screened at least once	112,092	68.9%	63.9%	69.3%	143,210	63.2%	52.7%	54.8%
Average Pap tests/person (age adjusted)	112,092	1.98 (1.94 – 2.00)	1.87 (1.86 – 1.89)	2.07 (2.05 – 2.09)	143,201	1.59 (1.56 – 1.62)	1.49 (1.48 – 1.50)	1.66 (1.65 – 1.67)
Average Pap tests/person excl. those who never screened (age-adjusted)	74,669	2.91 (2.87 – 2.94)	2.90 (2.89 – 2.91)	3.01 (3.00 – 3.02)	77,898	2.86 (2.83 – 2.89)	2.85 (2.83 – 2.86)	2.95 (2.94 – 2.97)

1. Claims made by health service providers for items on government subsidised Medicare Benefits Schedule (MBS), 2004-2011
 2. Participants screened through BreastScreen Australia do not appear as claims in MBS data
 3. Self reported responses to 45 and Up Study baseline questionnaire, excluding prior cancer cases
 4. Where frequency reported
 5. FOBT, colonoscopy or sigmoidoscopy
 6. Pap Test Register cervical screening and GP visitation data include those with prior cancer
- ** Some data include cases of self reported prior cancer (1) Sensitivity analyses of MBS claims and (2) All analyses of NSW Pap Test Register data

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Chapter 8: A comparison of cancer therapies in a cohort of farm, rural non-farm and urban residents aged 45 years and over in New South Wales

This chapter is a manuscript prepared for submission to a peer reviewed Australian journal.

Depczynski J, Dobbins T, Armstrong B, Lower T. Armstrong B. A comparison of cancer therapies in a cohort of Australian farm, rural non-farm and urban residents aged 45 years and over. Manuscript prepared for peer review.

8.1 Abstract

Objectives: To determine if selected therapies for prostate, breast and colorectal cancer vary by farm, rural non-farm or urban residence. **Design:** Data linkage of baseline survey information from the Sax Institutes' 45 and Up Study cohort with data from the New South Wales (NSW) Admitted Patients Data Collection (APDC) for 2006-2012. **Setting:** NSW. **Participants:** Farm, rural non-farm and urban residents aged 45 years and over. **Main outcome measures:** Surgical, chemotherapy, radiotherapy and brachytherapy procedures for those with a diagnosis of prostate, breast or colorectal cancer. Average distance to treating hospital and the odds of receiving selected therapies for each cancer were compared, controlling for selected variables. **Results:** Farm men were significantly more likely to have a prostatectomy for prostate cancer than rural non-farm men, but differences for breast and colorectal cancer surgery between resident groups were not significant. Farm and rural non-farm men had significantly lower odds of brachytherapy for prostate cancer than urban men; whilst farm and rural non-farm women were significantly less likely to have chemotherapy for breast cancer than urban women. Rural non-farm residents, were also significantly less likely to have chemotherapy for colorectal cancer than urban counterparts. Age, distance, income and health insurance factors contributed to differences in non-surgical care between groups. **Conclusion:** Cancer-related surgical services for breast and colorectal cancer were generally comparable between groups. Farm and rural non-farm residents may have been disadvantaged in relation to non-surgical therapies for prostate, breast and colorectal cancer compared to urban residents.

Keywords: Farm*, cancer, treatment, *therapy, rural, prostate, breast, colorectal, bowel

8.2 Introduction

Improved survival rates for prostate, breast and colorectal cancers in Australia over the past 30 years, has been largely attributed to better diagnostic methods, earlier detection and improvements in cancer treatment.¹ However, cancer treatments vary in complexity and availability to the general population. Poorer cancer survival in rural areas has been partly attributed to geographic and socio-economic difficulties rural people have in accessing optimal cancer treatments.² National data generally demonstrates decreased expenditure on specialist services per person with increasing remoteness from urban centres.³ However, it is not known if farm residents experience more or less difficulty accessing cancer services than other rural or urban people. We sought to determine if utilisation of therapies for prostate, breast and colorectal cancer, differed between farm, rural non-farm and urban people in New South Wales (NSW).

8.3 Methods

8.3.1 Datasets and linkage

Information from the Sax Institute's 45 and Up Study baseline questionnaire was used to define risk factors of interest and categorise participants into farm, rural and urban comparison groups. The cohort comprises 267,119 NSW residents aged 45 years or over enrolled between January 2006 and December 2009. Eligible individuals were randomly sampled from the enrolment database of the Australian Department of Human Services (formerly Medicare Australia), which provides near complete coverage of the NSW population. Details on 45 and Up Study methods are available elsewhere.⁴⁻⁵

The 45 and Up Study data were linked with corresponding data the NSW Admitted Patients Data Collection (APDC) for January 2006 - December 2012. The APDC records all inpatient separations from NSW public and private hospitals, multi-purpose services, private day procedure centres and public nursing homes.⁶ Linkage of records between datasets was conducted using probabilistic data linkage

methods, by the NSW Centre for Health Record Linkage (CHeReL). The CHeReL also provided geocode-derived distances between the non-disclosed residential address and treating hospital for each record.⁷

8.3.2 Definition of variables

‘Farm residents’ were defined as those who indicated they lived in a ‘house on farm’ on the 45 and Up Study baseline questionnaire. Rural ‘non-farm’ and urban residents were further defined using the Accessibility/Remoteness Index of Australia (ARIA+) from postcode of residence at recruitment.⁸ Those participants whose ARIA+ classification indicated they did not live in a ‘Major city’, excluding those who also specified that they lived in a ‘house on farm’, were defined as rural non-farm residents. The remaining ‘urban’ participants were those who lived in a ‘Major city’. Where ARIA+ was not recorded, allocation was determined by cross-checking with postcode of residence and distance to treating hospitals.

Variables of interest considered for inclusion in logistic regression models were age; distance from home address to treating hospital (kilometres); private health insurance with extras status; and annual household income \$70,000 or more. The latter was categorised to approximate levels above or below the NSW 2006 average annual household income of \$70,000.⁹

Cancer status was established where a prostate, breast or colorectal cancer diagnosis was recorded in any one of 55 diagnoses code fields of any APDC admission record over the period. Therapeutic procedures were identified within in any one of 51 procedure code fields on the APDC record. Diagnosis and procedure codes are based on the ICD10-AM and Medical Benefits Schedule (MBS) classification systems.⁶

Therapeutic procedures for each selected cancer were categorised into surgical, chemotherapy, radiotherapy and brachytherapy groupings. Surgical procedures for women with breast cancer were defined separately for mastectomies (procedure codes 31518-00 - 31524-00) and excision of breast

lesions (31500-00 - 31515-00). Surgical procedures for men with prostate cancer were defined by radical or laparoscopic prostatectomy (37209-00 - 37211-09). Surgeries for colorectal cancer for both men and women were defined by procedures relating to colectomies, resections or excision of colorectal tumours (32000-00 - 32069-00; 32099-00 - 32108-00). Trans-urethral resections of prostate, colonoscopies and aspirational biopsies were excluded from surgical procedure definitions. Brachytherapy implantation procedures (15327-00 - 15338-00) were compared for prostate cancer cases; and radiotherapy procedures (15100-00 - 15269-09) compared for those with a prostate, breast or colorectal cancer admission. Chemotherapy was limited to the administration of anti-neoplastic pharmacological agents only (96199-00, 96200-00, 96201-00, 96202-00, 96203-00, 96204-00, 96205-00, 96206-00, 96207-00, 96208-00, 96209-00). However, sensitivity analyses were conducted using wider categories of chemotherapy, such as administration of steroids, anti-infective agents or nutritional pharmacological therapies (96199-00 – 96209-09).

First procedure records for each person were used to calculate the average distance to hospital for each resident group. For logistic regression models, the average distance over all records for each person was used. Due to the magnitude of this variable, parameter estimates for distance to hospital are presented per 10km to assist with interpretation.

8.3.3 Analysis

Analysis was conducted using SAS 9.3.™ Frequencies and averages distances from home to hospital were calculated for farm, rural non-farm and urban residents who underwent the specified treatments for each cancer. Binary logistic regression was used to calculate adjusted odds ratios for selected treatments for each resident group. Variables with p-values < .25 on univariate analyses were included in the base model. Effect estimates and standard errors were compared between univariate and multivariable models; and variance inflation factors calculated to ensure collinearity did not exist between variables. Interactions between resident group and other factors were created and tested to assess effect

modification. Models were progressively reduced using a backward elimination approach (.05 level), removing non-significant variables and accounting for any non-significant confounders. Residual plots were examined to identify cases with undue influence in regression models. The difference between groups in the final adjusted odds ratio represents a difference not explained by factors left in the final model, but due to the effect of group residence or unknown factors.

8.4 Results

Tables 8.1 and 8.2 present the proportions of farm, rural non-farm and urban residents who underwent particular cancer therapies for each cancer type, the odds ratio for each therapy type and the average distance from home residence to hospital for a particular treatment.

Table 8.1: Procedures performed on farm, rural non-farm and urban men, who had a prostate or colorectal cancer diagnosis on any APDC admission record 2006-2012

Procedures for those with selected cancer diagnosis		Total n	Farm	Rural	Urban	Factors remaining in adjusted model
1. Prostate cancer						
1.1 Prostatectomy - radical or laproscopic (Procedure codes 37209-00 - 37211-00)						
n (%) of men with a diagnosis who had a procedure*		5,637	170 (45.8%)	901 (34.4%)	951 (35.9%)	• Age OR= 0.88 (0.87 – 0.89) • Private insurance with extras yes vs no OR= 1.17 (1.03 – 1.33)
Av. distance (km) (95%CI) from residence to health service for a first procedure		2,019	142.1 (122.4 – 161.8)	93.1 (85.9 – 100.4)	14.1 (12.8 – 15.5)	
Unadjusted OR (95%CI)		5,634	1.00	0.62 (0.50 – 0.78)	0.66 (0.53 – 0.83)	
Adjusted OR (95%CI)		5,634	1.00	0.74 (0.58 – 0.95)	0.83 (0.64 – 1.06)	
1.2 Chemotherapy - anti-neoplastic agents only (Procedure codes: 96199-00, 96200-00, 96201-00, 96202-00, 96203-00, 96204-00, 96205-00, 96206-00, 96207-00, 96208-00, 96209-00)						
n (%) of men with a diagnosis who had a procedure*		5,638	8 (2.2%)	78 (3.0%)	119 (4.5%)	• Age OR= 1.04 (1.03 – 1.06) • Private insurance with extras yes vs no OR= 1.56 (1.15 – 2.10) • [Av. distance to health service (per 10 km) was a non-significant confounder OR= 0.96 (0.93 – 1.00)]
Av. distance (km) (95%CI) from residence to health service for a first procedure		164	56.05 (22.0 – 90.1)	49.0 (30.0 – 68.0)	11.0 (8.0 – 14.1)	
Unadjusted OR (95%CI) for procedure		5,600	1.00	1.37 (0.66 – 2.86)	2.08 (1.01 – 4.30)	
Adjusted OR (95%CI) for procedure		5,600	1.00	1.14 (0.54 – 2.42)	1.33 (0.62 – 2.88)	
1.3 Radiotherapy (Procedure codes: 15100-00 - 15269-09)						
n (%) of men with a diagnosis who had a procedure*		5,638	8 (2.2%)	48 (1.8%)	81 (3.1%)	• Age OR=1.06 (1.04 – 1.08) • Private insurance with extras yes vs no OR= 0.61 (0.40 – 0.92) • [Annual household income over \$70,000/yr yes vs no OR= 0.90 (0.51– 1.60) a non-significant confounder]
Av. distance (km) (95%CI) from residence to health service for a first procedure		128	198.6 (82.3 – 314.8)	128.8 (86.8 – 170.8)	7.5 (6.2 – 8.7)	
Unadjusted OR (95%CI) for procedure [Rural vs. urban OR=0.59 (0.41 – 0.85)]		4,672	1.00	0.67 (0.29 – 1.50)	1.24 (0.56 – 2.73)	
Adjusted OR (95%CI) for procedure		4,672	1.00	0.54 (0.24-1.24)	1.01 (0.45 – 2.25)	

1.4	Brachytherapy - implantations (Procedure codes: 15327-00 - 15338-00)					
	n (%) of men with a cancer diagnosis who had a procedure*	5,637	18 (4.9%)	108 (4.1%)	185 (7.0%)	• Annual household income over \$70,000 yes vs no OR= 1.38 (1.01 – 1.77) • Private insurance with extras yes vs no OR= 1.83 (1.36 – 2.45) • Av. distance to health service (per 10 km) OR= 1.06 (1.04 – 1.08) • Cohort: rural non-farm vs. urban OR= 0.46 (0.34 – 0.63)
	Av. distance (km) (95%CI) from residence to health service for a first procedure	311	270.6 (182.0 – 359.2)	183.7 (160.4 – 206.9)	20.4 (16.0 – 24.9)	
	Unadjusted OR (95%CI) for procedure	4,641	1.00	1.03 (0.55 – 1.89)	1.70 (0.93 – 3.11)	
	Adjusted OR (95%CI) for procedure	4,641	1.00	1.34 (0.72 – 2.25)	2.90 (1.51 – 5.56)	
2.	Colorectal cancer					
2.1	Colorectal surgery – colectomies, resections, excisions (Procedure codes: 32000-00 – 32069-00, 32099-00 – 32108-00)					
	n (%) of men with diagnosis who had a procedure	1,878	76 (79.2%)	664 (72.4%)	642 (74.2%)	• Age OR= 0.99 (0.98 – 1.00)
	Av. distance (km) (95%CI) from residence to health service for a first procedure	1,367	78.1 (59.0 – 97.1)	54.0 (47.5 – 60.4)	9.6 (8.2 – 11.0)	
	Unadjusted OR (95%CI) for procedure	1,878	1.00	0.69 (0.41 – 1.15)	0.76 (0.45 – 1.27)	
	Adjusted OR (95%CI) for procedure	1,878	1.00	0.71 (0.42 – 1.18)	0.79 (0.47 – 1.32)	
2.2	Chemotherapy - anti-neoplastic agents only (Procedure codes: 96199-00, 96200-00, 96201-00, 96202-00, 96203-00, 96204-00, 96205-00, 96206-00, 96207-00, 96208-00, 96209-00)					
	n (%) of men with a cancer diagnosis who had a procedure*	1,878	9 (9.4%)	86 (9.4%)	145 (16.8%)	• Age OR= 0.98 (0.96 – 0.995) • Private insurance with extras yes vs no OR= 2.97 (2.11 – 4.17) • [Annual household income over \$70,000 yes vs no OR= 1.30 (0.89 – 1.90) ns] • [Av distance to health service (per 10 km) OR= 0.97 (0.93 - 1.02) a non-significant confounder] • Cohort: rural non-farm vs. urban OR= 0.62 (0.44– 0.90)
	Av. distance (km) (95%CI) from residence to health service for a first procedure	221	64.2 (0 – 156.5)	48.4 (30.4 – 66.5)	9.6 (7.8 – 11.4)	
	Unadjusted OR (95%CI) for procedure [Rural vs. urban OR=0.62 (0.49 – 0.78)]	1,510	1.00	0.80 (0.38 – 1.66)	1.60 (0.78 – 3.29)	
	Adjusted OR (95%CI) for procedure	1,510	1.00	0.78 (0.37 – 1.67)	1.25 (0.58 – 2.72)	
2.3	Radiotherapy (Procedure codes 15100-00 - 15269-09)					
	n (%) of men with diagnosis who had a procedure	1,878	<5	14 (1.5%)	25 (2.9%)	
	Av. distance (km) (95%CI) from residence to health service for a first procedure	37	168.2 (-)	125.6 (43.6 – 207.5)	8.3 (4.7 – 11.9)	

* Chi-square test of proportions between resident groups significant to .05 level.
 Bold text – Odds ratio significant compared to farm resident referent group to .05 level

Table 8.2: Procedures performed on farm, rural non-farm and urban women, who had a breast or colorectal cancer diagnosis on any APDC admission record 2006-2012

Procedures for those with selected cancer diagnosis	Total n	Farm	Rural	Urban	Factors remaining in adjusted model
1. Breast cancer					
1.1 Mastectomy (Procedure codes 31518-00 – 31527-00)					
% of women with diagnosis who had procedure	3,188	63 (35.0%)	542 (35.8%)	530 (35.5%)	• Age OR= 1.01 (1.00 – 1.01)
Av. distance (km) (95% CI) from residence to health service for first procedure	1,117	98.4 (67.8 – 128.9)	53.3 (46.2 – 60.3)	11.4 (9.6 – 13.2)	
Unadjusted OR (95% CI) for procedure	3,188	1.00	1.04 (0.75 – 1.43)	1.02 (0.74 – 1.41)	
Adjusted OR (95% CI) for procedure	3,188	1.00	1.01 (0.73 – 1.39)	0.99 (0.72 – 1.37)	
1.2 Excision, re-excision or open biopsy of lesion (Procedure codes 31500-00 – 31515-00)					
n / % of women with diagnosis who had procedure	3,188	112 (62.2%)	910 (60.1%)	893 (59.8%)	• Age OR= 0.98 (0.97 – 0.99) • Annual household income over \$70,000/yr yes vs no OR= 1.29 (1.04 – 1.60)
Av. distance (km) (95% CI) from residence to health service for first procedure	1,842	96.7 (76.9 – 116.4)	51.0 (46.0 – 56.1)	11.2 (9.6 – 12.9)	
Unadjusted OR (95% CI) for procedure	2,343	1.00	0.96 (0.66 – 1.40)	0.96 (0.66 – 1.39)	
Adjusted OR (95% CI) for procedure	2,343	1.00	1.06 (0.73 – 1.55)	1.03 (0.70 – 1.50)	

1.3 Chemotherapy - anti-neoplastic agents only (Procedure codes 96199-00, 96200-00, 96201-00, 96202-00, 96203-00, 96204-00, 96205-00, 96206-00, 96207-00, 96208-00, 96209-00)					
% of women with diagnosis who had procedure*	3,188	22 (12.2%)	234 (15.5%)	382 (25.6%)	• Age OR= 0.97 (0.96 – 0.98) • Annual household income over \$70,000/yr yes vs no OR= 1.37 (1.07 – 1.75) • Private health insurance with extras yes vs no OR= 2.42 (1.91 – 3.05) • Av distance to health service (per 10 km) OR= 0.97 (0.94 – 0.995) • Cohort: rural non-farm vs. urban OR= 0.70 (0.55 – 0.88)
Av. distance (km) (95% CI) from residence to health service for first procedure	624	57.4 (29.4 – 85.5)	49.9 (38.0 – 61.7)	9.5 (8.5 – 10.5)	
Unadjusted OR (95% CI) for procedure	2,330	1.00	1.38 (0.78 – 2.41)	2.58 (1.48 – 4.49)	
Adjusted OR (95% CI) for procedure	2,330	1.00	1.56 (0.88 – 2.77)	2.24 (1.25 – 4.04)	
1.4 Radiotherapy (Procedure codes: 15100-00 - 15269-09)					
% of women with diagnosis who had procedure	3,188	< 5 (<...%	32 (2.1%)	38 (2.5%)	
Av. distance (km) (95% CI) from residence to health service for first procedure	71	62.8 (-)	138.9 (83.9 – 193.9)	7.9 (5.3 – 10.5)	
2. Colorectal cancer					
2.1 Colorectal surgery – colectomies, resections & excisions (Procedure codes: 32000-00 – 32069-00, 32099-00 – 32108-00)					
% of women with diagnosis who had procedure	1,401	61 (76.3%)	549 (77.2%)	489 (80.2%)	• Nil
Av. distance (km) (95% CI) from residence to health service for first procedure	1,089	92.9 (63.4 – 122.4)	55.9 (48.4 – 63.4)	10.7 (7.0 – 14.5)	
Unadjusted OR (95% CI) for procedure	1,401	1.00	1.06 (0.61 – 1.82)	1.26 (0.73 – 2.19)	
Adjusted OR (95% CI) for procedure	1,401	1.00	1.06 (0.61 – 1.82)	1.26 (0.73 – 2.19)	

2.2 Chemotherapy – anti-neoplastic agents only (Procedure codes: 96199-00, 96200-00, 96201-00, 96202-00, 96203-00, 96204-00, 96205-00, 96206-00, 96207-00, 96208-00, 96209-00)					
% of women with diagnosis who had procedure*	1,401	9 (11.3%)	63 (8.9%)	95 (15.6%)	• Age OR= 0.95 (0.94 – 0.97) • Private insurance with extras yes vs no OR= 2.07 (1.35 – 3.16) • [Annual household income \$70,000 yes vs no OR= 1.16 (0.68 – 2.00) a non-significant confounder] • Cohort: rural non-farm vs. urban OR= 0.57 (0.37 – 0.88)
Av. distance (km) (95% CI) from residence to health service for first procedure	159	71.1 (20.3 – 122.0)	82.5 (49.5 – 115.5)	15.8 (2.9 – 28.6)	
Unadjusted OR (95% CI) for procedure	951	1.00	0.70 (0.29 – 1.61)	1.23 (0.53 – 2.84)	
Adjusted OR (95% CI) for procedure	951	1.00	0.84 (0.35 – 2.01)	1.47 (0.62 – 3.49)	
2.3 Radiotherapy (Procedure codes: 15100-00 - 15269-09)					
% of women with diagnosis who had procedure	1,401	<5	20 (2.8%)	12 (2.0%)	
Av. distance (km) (95% CI) from residence to health service for first procedure	71	162 (-)	98.8 (32.9 – 164.6)	13.0 (5.1 – 20.9)	

* Chi-square test of proportions between resident groups significant to .05 level.
 Bold text – Odds ratio significant compared to farm resident referent group to .05 level

8.4.1 Cancer therapies in men

- Prostate cancer

Farm men were significantly more likely to have a prostatectomy than rural non-farm men, with 35% higher odds of the procedure. Younger age and private health insurance with extras were positively associated with prostatectomy. The average distance to treating health service for prostatectomy was progressively longer from urban, to rural non-farm to farm resident group, but this was not a significant factor in the likelihood of having a prostatectomy. Urban men also had significantly less distance to travel for chemotherapy, radiotherapy or brachytherapy than the other two resident groups.

Small case numbers in the referent group affected calculation of odds ratios for both radiotherapy and chemotherapy for prostate cancer, resulting in wide confidence intervals that did not exclude the null value. With this in mind, farm men were more likely than rural non-farm men to have radiotherapy for prostate cancer. Conversely, farm men had lower odds of undergoing chemotherapy for prostate cancer than rural non-farm and urban men. Older age was positively associated with both radiotherapy and chemotherapy, private health insurance with extras was also positively associated with chemotherapy, but negatively associated with radiotherapy in the adjusted model.

In contrast, urban men were significantly more likely to have brachytherapy for prostate cancer. The odds of brachytherapy for urban men were almost three times that of farm men and twice that of rural non-farm men. Higher household income, greater average distance from treating hospital and private health insurance with extras, were positively associated with brachytherapy.

- Colorectal cancer

Farm men were more likely to have a surgical procedure for colorectal cancer than rural non-farm and urban men respectively, but differences between groups were not significant. Younger age was associated

with colorectal cancer surgery. Both farm and rural non-farm men travelled significantly further for colorectal surgery and chemotherapy than urban men.

Urban men had higher odds than both farm and rural non-farm men of undergoing chemotherapy for colorectal cancer, the latter being significant. Younger age was positively associated with chemotherapy. Men who had private health insurance with extras had almost three times the odds of having chemotherapy for colorectal cancer than those who did not.

8.4.2 Cancer treatments for women

- Breast cancer

There was little difference between residence groups for surgical procedures of the breast. Farm and rural non-farm women had a significantly greater distance to travel for surgical treatment than urban women, but distance was not associated with having surgery in final models. Older age was associated with mastectomy; but younger age and those with above median household incomes were more likely to have an excision of breast lesion.

Significantly, urban women had 2.2 times the odds of farm women of undergoing chemotherapy for breast cancer; and rural non-farm women 1.5 times the odds of farm women, although the latter was not significant. Younger age, above median household income and lesser average distance to travel, were positively associated with chemotherapy. Women with private health insurance with extras coverage had 2.4 times the odds of undergoing chemotherapy for breast cancer. Less than five farm women in the cohort underwent radiotherapy for breast cancer, so models were not generated. Urban women had significantly less distance to travel than other groups for breast cancer chemotherapy and radiotherapy.

- Colorectal cancer

There was little difference between farm, rural non-farm and urban women in the odds of undergoing colorectal surgery. The average distance to a treating hospital increased significantly from urban to rural non-farm, then farm groups, but again, this was not a significant factor in the likelihood of surgery.

Similar to findings for men, urban women were significantly more likely to undergo chemotherapy for colorectal cancer than rural non-farm women; and more likely than farm women, although the latter was not significant. Younger age was positively associated with chemotherapy; and women who had private health insurance had twice the odds of having chemotherapy for colorectal cancer than those who did not. Results for radiotherapy were inconclusive, with less than five cases in the farm group.

8.5 Discussion

There were no significant differences between resident groups in the odds of having surgery for breast or colorectal cancer. However, farm men were significantly more likely to have surgery for prostate cancer than rural non-farm men. In contrast, urban men were significantly more likely to have brachytherapy than the other groups. Urban men were also the most likely to have chemotherapy for prostate cancer, significantly more so than rural non-farm men. Likewise, urban women were significantly more likely to have chemotherapy for breast cancer than either of the other groups. Urban residents were also significantly more likely than rural non-farm counterparts to have chemotherapy for colorectal cancer. There were insufficient farm resident cases to examine likelihood of radiotherapy for breast and colorectal cancers; and whilst farm men were more likely to have radiotherapy for prostate cancer than rural non-farm men, this difference was not statistically significant.

Lesser distance to a treating hospital was a significant factor for breast cancer chemotherapy. Conversely, greater distance from health service, higher income and private health insurance with extras were associated with brachytherapy. Private health insurance with extras was also associated with

chemotherapy for prostate, breast and colorectal cancers; and with prostatectomy. Higher income was also positively associated with breast conserving surgery (excision of lesion) and chemotherapy, in breast cancer cases.

While farm specific data are unavailable, findings in the Australian literature for the provision of prostate, breast and colorectal cancer therapies to rural populations, are mixed. Some studies have reported comparable levels of cancer-related surgery and chemotherapy in urban and rural cancer patients.¹⁰⁻¹³ Others have reported lower rates of prostatectomy, breast conserving surgery, radiotherapy and chemotherapy in rural areas.^{2, 11-15}

Apart from socioeconomic difficulties related to travel, availability of specialist services can be an issue in rural areas.² Historically, limited access to specialist urologists was one reason suggested for lower rates of radical prostatectomy in rural areas in the 1990's;¹⁶⁻¹⁷ but farm and rural non-farm men were not disadvantaged compared to urban men in our study. Farm men underwent more prostatectomies, but this may have been because urban men were more likely to have chemotherapy and brachytherapy as alternative treatments. Brachytherapy is a viable alternative to radical prostatectomy for early prostate cancer, but is available in less than half of all Australian radiation oncology facilities.¹⁸ This may help to explain the higher uptake of this therapy amongst urban men in our study and the simultaneous reduced reliance on prostatectomy.

Interestingly, while urban residents had the least distance to travel for a first brachytherapy procedure; greater distance was associated with brachytherapy in the final model. There was no evidence of collinearity, so the apparent contradiction is likely related to derivation of the distance measure used in logistic regression modeling, where a dichotomous outcome for therapy was required. This calculated average distance to health services for all prostate cancer case records over the period, for those who did and those who did not have brachytherapy. Relating back to limited supply of radiation oncology facilities, those who had therapy were likely to have travelled further than the nearest health facility to have done

so, even in urban areas. That is, regardless of cohort residence, brachytherapy was associated with a greater distance to travel to obtain the service.

Surgery for colorectal cancer was reportedly lower amongst rural compared to urban residents in Queensland, but comparable in South Australia.^{10, 13} Early surgical management for breast cancer in rural and urban patients by an ACT facility was also reportedly comparable.¹² In contrast, the proportion of breast conserving surgeries or overall surgical procedures for breast cancer, was lower in rural women in Queensland and Western Australia, compared to urban counterparts.^{11, 13, 19} Our study did not have sufficient numbers to assess radiotherapy, which was also reportedly lower in rural women with breast cancer.¹¹⁻¹²

Chemotherapy was highest amongst urban people for all three cancers examined in our study. Delayed or lower odds of chemotherapy for breast and colorectal cancer patients in rural NSW have been reported previously.¹⁴⁻¹⁵ In contrast, studies from South Australia and Western Australia have reported similar levels of chemotherapy administration for breast and colorectal cancer patients in urban and rural patients.¹⁰⁻¹¹ In these states, more centralised treatment models have developed to service sparse populations outside capital cities, which contrasts with rural NSW where there are sizeable regional populations.¹⁰

Findings for chemotherapy and radiotherapy in our study should be considered with some caution, due to low case numbers, impacting upon confidence intervals and the potential significance of differences observed. Validation studies have also found these procedures to be underreported in the APDC; and prostate cancer therapies less accurately recorded for non-urban cases. Potentially, the latter could lead to a positive bias toward higher odds of prostate cancer therapies amongst urban men. In contrast, surgical treatments and brachytherapies are usually well captured.²⁰⁻²¹

Other limitations include the 45 and Up Study cohort not being completely representative of the NSW population, although linkage with population datasets has shown that biases are limited.^{4, 22} Also, the definition of a 'farm resident' in this study was also open to respondents' interpretation of a 'farm' and could include small holdings used for commercial, recreational or both purposes. Consequently, exposures, practices and lifestyles of farm residents may vary or are not clearly defined.²³ This could affect the representativeness of sub-groups and internal validity of comparisons made. However, misclassification errors are likely to be non-differential and independent of other risk factors, leading to a null bias and underestimation of relationships between farm residence and cancer screening.

Notwithstanding these limitations, our study found that cancer-related surgical services were generally comparable between farm, rural non-farm and urban residents for breast and colorectal cancers. Farm men were more likely to have a prostatectomy, but this may have been related to higher utilisation of chemotherapy and brachytherapy as alternative treatments by urban men. Age, distance to health services, income and health insurance factors contributed to differences in non-surgical care between groups.

The significantly higher utilisation of non-surgical services by urban residents in this study (up to 2012), supports earlier reports of disadvantage in specialist cancer services in rural areas.² In addition, our study suggests the disadvantage is similar across farm and rural non-farm resident groups. Challenges for oncology service provision in rural areas include rural demographics, communications technology, recruitment and retention of technically qualified personnel and the planning and coordination of surgical, pathology and oncology services.^{10, 14, 18, 24} Ongoing development of the Rural Cancer Centres initiative, telemedicine and CanNET cancer networking services, are likely to address rural-urban imbalances and improve the accessibility, quality and coordination of rural cancer services in the years to come.²⁴⁻²⁵

8.6 Acknowledgements

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8.7 Appendix

Table 8.3: Comparison of chemotherapy procedures performed on farm, rural non-farm and urban men with a prostate or colorectal cancer diagnosis on any hospital admission record 2006-2012, using different APDC chemotherapy code ranges

Chemotherapy procedures for those with selected cancer	Anti-neoplastic agents only (main analyses) (Procedure codes: 96199-00, 96200-00, 96201-00, 96202-00, 96203-00, 96204-00, 96205-00, 96206-00, 96207-00, 96208-00, 96209-00)					All chemotherapy codes, including steroids, anti-infectives and others (sensitivity analyses) (Procedure codes: 96199-00 - 96209-00)				
	Total n	Farm	Rural	Urban	Factors remaining in adjusted model	Total n	Farm	Rural	Urban	Factors remaining in adjusted model
Prostate cancer										
n (%) of men with a diagnosis who had a procedure	5,638	8 (2.2%)	78 (3.0%)	119 (4.5%)	- Age OR= 1.04 (1.03 – 1.06) - Private insurance with extras yes vs. no OR= 1.56 (1.15 – 2.10) [Av. distance to health service (per 10 km) OR= 0.96 (0.93 – 1.00) a non-significant confounder]	5,638	15 (4.0%)	187 (7.1%)	201 (7.6%)	- Age OR= 1.05 (1.03 – 1.06) [Household income over \$70,000/yr yes vs. no OR= 1.11 (0.82 – 1.50) a non-significant confounder] [Av. distance to health service (per 10 km) OR= 0.99 (0.99 – 1.00) a non-significant confounder]
Av. distance (km) (95%CI) from residence to health service for a first procedure	164	56.05 (22.0 – 90.1)	49.0 (30.0 – 68.0)	11.0 (8.0 – 14.1)		292	44.9 (24.6 – 65.2)	52.9 (35.9 – 70.0)	11.0 (8.8 – 13.1)	
Adjusted OR (95%CI) for procedure	5,600	1.00	1.14 (0.54 – 2.42)	1.33 (0.62 – 2.88)		4,665	1.00	1.36 (0.76 – 2.45)	1.20 (0.66 – 2.18)	
Colorectal cancer										
n (%) of men with a cancer diagnosis who had a procedure	1,878	9 (9.4%)	86 (9.4%)	145 (16.8%)	- Age OR= 0.98 (0.96 – 0.995) - Private insurance with extras yes vs. no OR= 2.97 (2.11 – 4.17) [Annual household income over \$70,000/yr yes vs. no OR= 1.30 (0.89 – 1.90) a non-significant confounder] [Av distance to health service (per 10 km) OR= 0.97 (0.93 - 1.02) a non- significant confounder] - Cohort: rural non-farm vs. urban OR= 0.62 (0.44– 0.90)	1,878	17 (17.7%)	156 (17.0%)	215 (24.9%)	- Private insurance with extras yes vs. no OR= 1.98 (1.57 – 2.49) - Cohort: rural non-farm vs urban OR= 0.67 (0.53– 0.84)
Av. distance (km) (95%CI) from residence to health service for a first procedure	221	64.2 (0 – 156.5)	48.4 (30.4 – 66.5)	9.6 (7.8 – 11.4)		227	91.8 (25.0 – 158.6)	46.9 (31.3 – 62.4)	9.1 (7.7 – 10.5)	
Adjusted OR (95%CI) for procedure	1,510	1.00	0.78 (0.37 – 1.67)	1.25 (0.58 – 2.72)		1,877	1.00	0.99 (0.57 – 1.73)	1.49 (0.86 – 2.58)	

Table 8.4: Comparison of chemotherapy procedures performed on farm, rural non-farm and urban women with a breast or colorectal cancer diagnosis on any hospital admission record 2006-2012, using different APDC chemotherapy code ranges

Chemotherapy procedures for those with selected cancer	Anti-neoplastic agents only (main analyses) (Procedure codes: 96199-00, 96200-00, 96201-00, 96202-00, 96203-00, 96204-00, 96205-00, 96206-00, 96207-00, 96208-00, 96209-00)					All chemotherapy codes, including steroids, anti-infectives and others (sensitivity analyses) (Procedure codes: 96199-00 - 96209-00)				
	Total n	Farm	Rural	Urban	Factors remaining in adjusted model	Total n	Farm	Rural	Urban	Factors remaining in adjusted model
Breast cancer										
n (%) of women with a diagnosis who had a procedure	3,188	22 (12.2%)	234 (15.5%)	382 (25.6%)	- Age OR= 0.97 (0.96 – 0.98) - Annual household income over \$70,000/yr yes vs no OR= 1.37 (1.07– 1.75) - Private health insurance with extras yes vs no OR= 2.42 (1.91 – 3.05) - Av distance to health service (per 10 km) OR= 0.97 (0.94 – 0.995) - Cohort: rural non-farm vs urban OR =0.70 (0.55 – 0.88)	3,188	27 (15.0%)	272 (18.0%)	416 (27.8%)	- Age OR=0.98 (0.97 – 0.99) [Annual household income over \$70,000/yr yes vs no OR= 1.39 (1.09– 1.76) a non-significant confounder] - Private health insurance with extras yes vs no OR= 2.22 (1.79 – 2.77) - Cohort: rural non-farm vs urban OR=0.68 (0.55 – 0.85)
Av. distance (km) (95%CI) from residence to health service for a first procedure	624	57.4 (29.4 – 85.5)	49.9 (38.0 – 61.7)	9.5 (8.5 – 10.5)		770	58.9 (34.2 – 83.6)	46.8 (35.9 – 57.8)	9.4 (8.4 – 10.4)	
Adjusted OR (95%CI) for procedure	2,330	1.00	1.56 (0.88 – 2.77)	2.24 (1.25 – 4.04)		2,342	1.00	1.62 (0.95 – 2.75)	2.36 (1.40 – 4.00)	
Colorectal cancer										
n (%) of women with a cancer diagnosis who had a procedure	1,401	9 (11.3%)	63 (8.9%)	95 (15.6%)	- Age OR= 0.95 (0.94 – 0.97) - Private insurance with extras yes vs no OR= 2.07 (1.35 – 3.16) [Annual household income \$70,000/yr yes vs no OR= 1.16 (0.68 – 2.00) a non-significant confounder] - Cohort: rural non-farm vs urban OR= 0.57 (0.37 – 0.88)	1,401	12 (15.0%)	128 (18.0%)	126 (20.7%)	- Age OR=0.98 (0.96 – 0.99) - Private insurance with extras yes vs no OR= 1.68 (1.20 – 2.36) [Annual household income \$70,000/yr yes vs no OR= 0.97 (0.60 – 1.59) a non-significant confounder]
Av. distance (km) (95%CI) from residence to health service for a first procedure	159	71.1 (20.3 – 122.0)	82.5 (49.5 – 115.5)	15.8 (2.9 – 28.6)		221	67.3 (17.9 – 110.8)	57.1 (35.9 – 78.3)	14.3 (3.7 – 24.8)	
Adjusted OR (95%CI) for procedure	951	1.00	0.84 (0.35 – 2.01)	1.47 (0.62 – 3.49)		951	1.00	1.07 (0.51 – 2.23)	1.28 (0.61 – 2.68)	

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Chapter 9: Discussion

9.1 Context

The central aim of this study was to compare cancer indicators between Australian farm residents and their non-farm and urban counterparts. Information on the comparative cancer profile of Australian farm residents has the potential to contribute to the evidence base on which rural health policy and resourcing decisions are made. Farmers and farm families have particular characteristics regarding their age profile, employment, lifestyle, potential environmental exposures and socio-economic conditions. This has raised questions elsewhere as to whether farmers have a different cancer profile to other rural or urban people. The majority of farms and farm families in Australia are located in inner and outer regional areas; so they are likely to share some characteristics of the larger rural population of which they form a part.¹⁻²

An overview of cancer in rural Australia provided background context to the research. Generally, urban residents had lower cancer incidence and mortality than rural people. Regional areas tended to have the highest incidence and mortality from melanoma, prostate and colorectal cancer. Remote and very remote areas tended to have the highest incidence and mortality for lung cancer and the highest mortality for all cancers. Patterns for breast cancer and lymphoma by remoteness category were variable.

Measures of cancer screening and treatments can provide some insight into health service access and utilisation in different areas. Compared to urban areas, there are some indications of higher health system utilisation and screening in regional areas, which then fall as areas become more remote. A range of socio-demographic characteristics, rather than geography itself may be important in influencing general health and cancer indicators. In rural areas these include older age, higher levels of risky health behaviours, income and educational disadvantage, lower utilisation of preventative health services, limited access to some healthcare services; and a higher proportion

Indigenous Australians.^{1, 3-9} Geographic distance may also contribute both to delays in diagnosis and decisions regarding cancer treatment.^{1 10}

Given limited Australian studies of cancer risk in farmers, a review of the international literature was conducted. The strength of evidence for an excess risk in farm groups in the review of studies published since 2003 was generally weaker than in previous reviews. Most studies in our review reported neutral findings. Overall deficits in all cancer, lung and colorectal cancer risk were suggested, similar to previous reviews. A deficit or neutral risk of breast cancer and neutral risk of melanoma was also suggested; with mainly neutral but some excess risk suggested for lymphohaematopoietic cancers. Previous reviews and one Australian study had reported higher prostate cancer risk in farmers, so this was the subject of a specific review for this Project, published in 2014. Essentially, neutral or mixed findings were apparent for prostate cancer risk in farmers, depending on study methods and location, such that the overall evidence for elevated prostate cancer risk in farmers was also weak.

The cancer risk profile of farmers may have improved in recent years, but review findings may have been a result of greater control for confounders in more recent studies. In any case, there was little evidence for an excess risk in farmers for most cancers, with the possible exception of prostate and some lymphohaematopoietic cancers, for which the evidence was still weak. There was insufficient evidence on differences in cancer stage at diagnosis or treatment between farm and non-farm groups; and the evidence on differential cancer screening practices was also low or lacking.

Information on Australian farm residents was extremely limited and there was very little information on health service related factors. This was the background to the series of data linkage studies undertaken in this Project, to determine if there were differences between NSW farm residents, compared to non-farm rural and urban residents, in cancer incidence or mortality; stage at diagnosis, screening and selected cancer therapies; or in common risk factors that might be

associated with these cancers. The 45 and Up Study cohort enabled identification of farm residents, not otherwise identifiable in standard population-wide health reports. Comparison of cancer indicators between groups was then made possible through data linkage to administrative health datasets.

9.2 Findings and contribution of component studies to the literature

With no previous Australian and very few international studies comparing cancer indicators between farm, rural non-farm and urban residents, this series of studies offers a unique contribution to the cancer epidemiology literature.

9.2.1 Mortality

The first study examined cancer mortality and cancer risk factors in farm, rural non-farm and urban residents of the 45 and Up Study cohort. Data for the cohort were linked with NSW death registrations and cause of death data for 2006 - 2012. Direct age-standardised mortality ratios and adjusted hazard ratios were compared between groups for all cancers, prostate, breast, lung and colorectal cancers, NHL and melanoma.

Farm, rural non-farm and urban residents in the cohort differed in a range of characteristics, but most notably, farm residents were younger than the other cohorts. Therefore, it was important to control for age in all comparisons. Differences in smoking status, alcohol consumption, overweight/obesity, tannability and family history of selected cancers were generally small. Farm residents had noticeably higher average sun exposure and red meat consumption; and considerably more urban residents had annual household incomes over the median level.

Consistent with the direction of review findings, farm residents had lower all cancer mortality risk than rural non-farm or urban residents, but confidence intervals for fully adjusted measures did not exclude unity. There was a significant deficit in the all cancer SMR in farm men compared to

rural non-farm and urban men. Farm men also had a considerable deficit in colorectal cancer mortality, although this was not significant. Also consistent with review trends, there were slight non-significant elevations in melanoma and prostate cancer mortality in farm men. There was also a non-significant reduction in NHL mortality risk in farm men. The latter was consistent with an overall neutral review finding, although the review more commonly reported slight elevations rather than deficit risk in farmers.

Farm women had a similar all cancer SMR to farm men, although differences between groups were not significant. In contrast, breast cancer SMR in farm women was significantly lower than unity; and mortality hazard two-thirds of and significantly lower than rural non-farm women, when controlling for other risk factors. Findings for lower melanoma risk were tempered by low numbers; and while colorectal and lung cancer mortality was also lower in farm women, this was not significant.

Risk factors of particular interest were smoking and sun exposure. Current smokers had 16 - 18 times the adjusted hazard of mortality as that of never smokers; and risks of melanoma and several other cancers were higher amongst those with very limited sun exposure of less than 1 hour/day, compared to those with regular exposure of 1-4 hours per day.

Overall, farm residents in this cohort had a neutral or non-significantly lower cancer mortality risk profile compared to rural non-farm and urban residents.

9.2.2 Incidence

The second study compared cancer incidence and linked 45 and Up Study cohort data to NSW Cancer Registry data for the years 2006 - 2009. Direct age-standardised incidence ratios and hazard ratios were compared for all cancer, prostate, breast and colorectal cancers, melanoma and NHL.

The adjusted hazard ratio for all cancer incidence in farm men and women was around 10% lower than in rural non-farm and urban counterparts; and significantly lower than combined rural non-farm and urban groups. Farm women also had a significantly lower adjusted all cancer hazard than rural non-farm women. Differences in all cancer incidence were mainly due to lower lung cancer incidence risk in farm residents. Although not significant in itself, lung cancer incidence and likelihood in farm residents were one half to two-thirds that of rural non-farm and urban residents. The direction of findings for all cancer and lung cancer, were largely consistent with review findings.

Farm women had by far the lowest melanoma incidence, being highly significant, but caution is advised due to low case numbers. There was little evidence of any difference in incidence of breast or colorectal cancers; and results were inconclusive for NHL.

Regarding risk factors, hazard ratios for lung cancer were 18 times higher in men and 9 times higher in women who were current compared to never smokers. Minimal sun exposure of less than an hour a day was associated with higher hazard for several cancers, including melanoma. Whilst there is some evidence of this effect elsewhere,¹¹⁻¹⁴ it is feasible that minimal sun exposure may have also been a proxy for limited physical activity in this cohort.

Similar to mortality, findings suggest farm residents in this cohort were not at a disadvantage regarding risk of prostate, breast, lung and colorectal cancers, melanoma or NHL; with similar or non-significantly reduced risk for most of the cancers examined.

9.2.3 Stage at cancer diagnosis

The third study in the series also used NSW Cancer Registry records from 2006-2009, to compare the adjusted odds ratio of non-localised cancer stage between resident groups for prostate, breast and colorectal cancers. Caution was advised with results for prostate cancer, as one third of cases in the NSW Cancer Registry had no recorded stage. Rural non-farm men were significantly less likely

than urban men to be diagnosed at later stage of prostate cancer, while farm men were not disadvantaged compared to either group. In contrast, farm men had a greater proportion and twice the odds of the other groups of being diagnosed with later stage colorectal cancer, although confidence intervals did not exclude unity.

Farm women were least likely to be diagnosed with later stage breast cancer; and less likely than rural non-farm women to have later stage colorectal cancer, although results were not significant. Higher household income was associated with later stage breast and prostate cancer, but private health insurance with extras associated with earlier stage prostate cancer. The different patterns of risk, especially between farm and rural non-farm men were not explained by the risk factors assessed.

Our findings for prostate cancer in men and for breast and colorectal cancer in women were similar to the limited evidence in the literature on cancer stage in farm versus non-farm groups.¹⁵⁻¹⁶ When considering rural versus urban patterns, findings were also consistent with other studies in Australia for breast cancer and colorectal cancer.¹⁷⁻¹⁹ Although not significant, the higher odds for later colorectal cancer in farm men compared to both urban and rural non-farm men warrants further investigation, as it may have implications for screening and earlier or more appropriate diagnostic services in rural areas.

9.2.4 Screening

The fourth study compared cancer screening practices between resident groups for participants under 75 years in those without prior cancer. Self-report data from the 45 and Up Study baseline survey were compared for prostate, breast and colorectal cancer. Data linkage with the MBS enabled comparison of the average number of screening tests and General Practitioner visits per person (age-adjusted), claimed by service providers for the 2004-2011 period. For cervical cancer

screening, data were linked with NSW Pap Test Register records for 2006-2012. Age-adjusted comparisons were made using general linear regression and logistic regression.

Farm residents were significantly least likely to visit a GP, but screening practices between farm and rural non-farm residents were generally similar. Urban residents, however, had significantly more prostate specific antigen (PSA) tests, Pap tests, mammograms and colonoscopies than either of the other groups; and more likely to report ever having a mammogram or colonoscopy. In contrast, farm and rural non-farm residents had significantly more FOBTs than urban counterparts; and were around one third more likely than urban residents to report ever having a FOBT. Farm residents were most and significantly more likely than rural non-farm men to report ever having a PSA test - and both rural groups significantly more likely than urban counterparts to report ever having or 'any' form of colorectal screening test.

Overall, screening practices of farm and rural non-farm residents were similar. However, results suggested that compared to urban residents, both rural groups had lower utilisation and perhaps reduced access to procedural screening services. Other Australian studies have reported lower cancer screening rates in rural compared to urban areas,²⁰⁻²¹ although participation in population-based breast, cervical and colorectal cancer screening programs, have generally been higher in regional rather than urban areas.²²⁻²⁴ Lack of access to specialist colonoscopy services may have explained the relatively higher usage of FOBT's by farm and rural residents.

9.2.5 Cancer therapies

The fifth and final study of the series examined differences in common cancer therapies for prostate, breast and colorectal cancers. The 45 and Up Study data were linked with data from the NSW Admitted Patients Data Collection (APDC) for 2006-2012. Surgical, chemotherapy, radiotherapy and brachytherapy procedures were compared for those with a diagnosis of prostate, breast or colorectal cancer over the period. Average distance to treating hospital for each therapy was

determined and logistic regression used to compare the odds of receiving treatment, controlling for age, income and private health insurance status.

Farm men were significantly more likely to have a prostatectomy than rural non-farm men, but differences for breast and colorectal cancer surgery were not significant. Farm and rural non-farm residents were significantly less likely to have brachytherapy; and had lower odds of chemotherapy procedures than urban counterparts. In particular, farm and rural non-farm women were significantly less likely to have chemotherapy for breast cancer than urban women. Rural non-farm residents were also significantly less likely to have chemotherapy for colorectal cancer; whilst urban men had almost three times the odds of having brachytherapy. Age, distance, income and health insurance factors contributed to differences in non-surgical care between groups.

In general, cancer-related surgical services for breast and colorectal cancer were comparable between groups. Findings for chemotherapy and radiotherapy in our study should be considered with caution due to the small number of farm cases used to calculate odds ratios, present in the data set. However, findings suggest farm and rural non-farm residents may have been disadvantaged in relation to non-surgical therapies for prostate, breast and colorectal cancer. This is consistent with findings of other studies on rural versus urban cancer services.²⁵⁻²⁸ Difficulties for rural cancer service provision include communications technology, recruitment and retention of technically qualified personnel and the planning and coordination of services.^{25, 29} There was no comparable farm specific data in the literature with which to compare our results for higher odds of prostatectomy in farm versus rural non-farm men, but this shall be discussed in light of our own earlier findings on mortality, incidence, stage and screening for this cohort, in the following section.

9.3 Patterns in cancer indicators across studies

This section aims to examine the pattern of cancer indicators across studies. Firstly, it needs to be reiterated that most differences in cancer indicators between resident groups, were not

statistically significant; so inferences are largely exploratory. However, it is logical and indeed possible that some of the indicators examined in each study separately, may be having an impact upon other indicators, for any one cancer.

- Prostate cancer

For prostate cancer, there was little difference between groups in cancer incidence risk; and whilst there were some differences between groups in mortality and stage of diagnosis, most confidence intervals did not exclude unity. Acknowledging this, SMR was 20-25% higher and adjusted hazard 10-20% higher in farm residents compared to other groups. If indeed true, this pattern could potentially reflect less effective or perhaps later detection of prostate cancer in farmers compared to others. Stage at prostate cancer diagnosis was similar between farm and urban men, but the adjusted odds for rural non-farm men was two-thirds that of other men. This may have contributed to the slightly elevated mortality in farm residents, at least relative to rural non-farm men. Unfortunately, the high level of unrecorded stage for prostate cancers in the NSW CR data, does limit inferences that can be made of how stage at diagnosis might influence other indicators.

Cancer screening may provide some insight as to whether prostate cancers were being detected at an earlier stage, when treatment is likely to be more effective. Results for PSA testing in the MBS suggested PSA screening was significantly lower in farm compared to urban men, but similar to rural men. So, while farm men were more likely to be diagnosed at later stage than rural non-farm men, (although not significantly), screening practices appear to be similar between these two groups. Conversely, screening was significantly lower in farm men than urban men, yet these had similar stage of diagnosis profiles. These seemingly unrelated associations for screening and stage, may be a symptom of the unrecorded stage component and low case numbers in the farm group; or could suggest that less comprehensive screening is not necessarily linked to higher mortality.

While cognizant that the low case numbers in the farm group impacts upon the power to detect a difference between groups for some analyses, the other factor examined that may have been associated with higher mortality in the face of similar incidence rates, were cancer treatments. Farm men had significantly greater odds of prostatectomy than rural non-farm men, and non-significantly greater odds than urban men. Clinically, prostatectomy is a common therapy for early prostate cancer, with the aim of removing the lesion before it spreads beyond the prostate gland and adjacent tissues. Chemotherapy, radiotherapy and brachytherapy regimes may or may not be provided as an additional support to surgical measures. Alternatively, non-surgical therapies are often used without surgery in advanced prostate cancer.³⁰⁻³¹

Relating treatments back to stage data, while farm and urban men had similar odds for later stage diagnosis, farm men were far less likely to have chemotherapy or brachytherapy. Significantly, the odds of brachytherapy in farm men were only one third that of urban men; and a non-significant three-quarters that of rural men. Therefore, whilst acknowledging confidence intervals for prostate cancer mortality risk did not exclude unity, can the higher risk of mortality in farm men be partly explained by fewer farm men having non-surgical or combined therapies for prostate cancer than other men?

- Breast cancer in women

Differences in incidence of breast cancer between groups were not significant, but farm women had slightly lower adjusted hazard and 13-14% lower SIR than either of the other two groups. Several common cancer risk factors were controlled for, including sun exposure, which was significantly higher amongst farm women in this cohort and has been linked to lower breast cancer risk elsewhere.¹³⁻¹⁴ However, as previously outlined, higher sun exposure may also be acting as a proxy for greater physical activity. This is known to be protective against breast cancer, but was not controlled for in this study.³²

The difference between groups in breast cancer was more prominent for mortality, where significantly, farm women had a lower SMR than other groups; and lower adjusted hazard ratio than rural non-farm women. When examining stage at diagnosis, farm women also had the lowest odds of being diagnosed at later stage, though non-significant. This may also contribute to lower mortality in farm women. The factors underpinning why farm women were less likely to be diagnosed at later stage are unclear. Both MBS and self-reported screening results suggest breast cancer screening in this cohort was actually higher amongst urban women; and differences in frequency were not significant. While MBS data excluded participants of the free mobile Breastscreen program promoted particularly well in rural areas, self-reported screening was also lower amongst farm women. Screening patterns do not appear to adequately explain why farm women had lower mortality or odds of later stage diagnosis although low farm case numbers were also a likely issue.

There was very little difference in the adjusted odds of breast cancer surgery between groups, whether for breast conserving excision of a lesion, or radical mastectomy. However, farm women were much less likely to undergo chemotherapy for breast cancer, with odds two thirds that of rural non-farm women and significantly less than half those of urban women. Chemotherapy is not necessarily indicated for women who are at early stage of disease, unless tumours are larger or the risk of breast cancer recurrence is high.³³ This may well fit with the greater odds of earlier stage breast cancer diagnosis in farm women. Whilst clinical treatment decisions are made on a case by case basis, this may be one reason farm women as a group had less chemotherapy, rather than there being a lack of access to breast cancer chemotherapy services. If the latter was the case, the odds of chemotherapy and mortality risk of farm and rural non-farm women would be similar, but they are not. Conversely, both the odds of chemotherapy and risk of mortality from breast cancer for farm women was significantly lower than for rural non-farm counterparts.

For this cohort, although not significant, slightly lower incidence and odds of later stage diagnosis of breast cancer in farm women; together with significantly lower rates of chemotherapy suggestive of cancers treated at an earlier stage, may all combine to produce a significantly lower breast cancer mortality profile in farm women. The role of screening in leading to earlier diagnosis was not apparent in the data; but Breastscreen monitoring reports and previous studies of screening in this cohort suggest participation is better in regional areas.³⁴⁻³⁵ Others have reported a 15-30% reduction in mortality in women aged 50-69 years who screen for breast cancer.³⁶ Promotion of Breastscreen has been strongly supported in rural areas by community organisations, including the Country Womens Association. Farm women may have benefited most from higher rates of breast screening in regional Australia.

- Colorectal cancer in women

There was little difference in the SIR or hazard ratio for incidence of colorectal cancer in women. However, colorectal cancer mortality in farm women was around two-thirds that of other groups, although this was not a significant difference. As with breast cancer, it is possible that farm women were being diagnosed and treated at an earlier stage, compared to rural non-farm women at least, even though FOBT screening patterns were similar for the two rural groups. Farm and rural non-farm women, both had significantly more FOBT's than urban women, but colonoscopies were significantly more likely amongst urban women than either rural group, suggestive of higher access to this service in urban areas.

For surgery, farm and rural non-farm women had lower odds of surgery than urban women, although not significantly so. The odds of chemotherapy for both farm and rural non-farm women were around two-thirds that of urban women, being significantly lower for rural non-farm women. This scenario is suggestive of a disadvantage for rural women in access to both surgical and chemotherapy services, although again, small numbers may be responsible for observed patterns.

Lower colorectal cancer mortality in farm women remains unexplained, although compared to rural non-farm women, earlier stage of diagnosis may be a contributing factor, despite similar screening and treatment patterns between these two groups. As suggested for breast cancer mortality, the protective effect of greater levels of physical activity amongst farm women, may have contributed to better survival from colorectal cancer.³² It cannot be ruled out however, that lower mortality amongst farm women, was a consequence of the relatively low case numbers in the farm group and may have been due to chance. A longer follow-up time likely to produce more stable odds ratios for comparative purposes.

- Colorectal cancer in men

There were no significant differences in incidence or mortality due to colorectal cancer between groups of men, although the hazard for incidence in farm men was slightly lower than rural men; and mortality hazard in farm men around two-thirds that of other groups. This is despite the odds of later stage diagnosis in farm men, being twice that of rural non-farm and urban men (though not significant); and screening patterns in farm men being similar to rural non-farm men.

Screening patterns for colorectal cancer in men were similar to women. That is, farm men had significantly more FOBT's than urban counterparts, but a similar likelihood to rural non-farm men. Colonoscopies were significantly higher amongst urban men than the rural groups, suggestive of higher access to this service in urban areas. It is also possible that urban men may be having suspect lesions removed during colonoscopy as they are detected, without requiring more invasive surgery at a later time.

Although not significant, odds of colorectal cancer surgery for farm men were around a third higher in farm men than other groups. In contrast, the odds of chemotherapy were lower in farm and rural non-farm men than urban men, the latter significantly so. This suggests perhaps more

limited access to chemotherapy treatment options in rural areas. Again, whilst farm case numbers were small and most differences not significant, taken together, the greater odds of later stage diagnosis in farm men and lower odds of chemotherapy for both farm and rural men, may be a concern for provision of early colorectal cancer diagnosis and care in rural areas. However, the question remains: if farm men have greater chance of later stage diagnosis and both farm and rural non-farm men have less optimal treatments, why does this not translate to higher rates of mortality? This may be an artefact of data limitations in this study, or perhaps as for women, lower mortality observed in farm men may be a consequence of factors affecting survival other than stage and treatments that were not controlled for in this study, such as physical activity.

- Incidence and mortality due to lung cancer, melanoma and NHL

There were insufficient newly diagnosed cases of lung cancer, melanoma and NHL in the farm group to examine and compare stage at diagnosis or treatments in this study. However, comparing incidence and mortality for these cancers may provide insights on what may be happening at a group level. However, considering the impact of small case numbers and wide confidence intervals upon the strength of conclusions, discussion should be considered exploratory.

For lung cancer, the SIR of farm men was considerably one third lower than rural non-farm men, with this difference maintained for SMR. When controlling for other risk factors farm men still had around 15% lower adjusted hazard than rural non-farm men for both incidence and mortality. Maintenance of these relative group differences between incidence and mortality, controlling for common risk factors, suggests that the combined effects of stage at diagnosis and /or treatment on mortality risk, were likely to be similar for the two rural groups. In contrast, the gap between SIR / incidence hazard and SMR / mortality hazard for urban men closed or 'improved' relative to other men. This suggests either earlier diagnosis or better access to specialist treatment for lung cancer in

urban areas, as has been previously proposed.³⁷ Conversely, low case numbers may have been responsible for the patterns observed.

Similar to farm men, farm women had considerably lower incidence and hazard ratios, being around half as likely to be diagnosed as other women. However, whilst farm women still had lower mortality, their relative advantage from SIR to SMR had halved; and the adjusted hazard had become similar to rural non-farm women; although still lower than urban women. The drop in the initial advantage of farm women between indicators is similar to farm men, so might suggest a similar phenomenon regarding less access to cancer treatments. If that were the case, one would expect corresponding disadvantage for rural non-farm women - which does not appear to be the case. Again, only a small number of farm women were diagnosed with lung cancer in the period covered by this study, so caution is advised with incidence findings.

For melanoma, the differences in adjusted hazard ratios for incidence and mortality between groups were maintained, with farm men having around 10% higher risk. Farm women had a significant mortality advantage, but there was little difference to other groups in incidence. Caution is again advised with interpretation due to low case numbers.

Differences between groups in SIR and SMR for NHL in men were maintained, with farm men having the lowest rates and urban the highest. For women, differences were also maintained between groups for SIR and SMR. Farm women had the highest SIR, but SMR was even higher. Again case numbers were low in the farm group, so caution is advised in the degree of difference, if not the rank. For both melanoma and NHL, in light of low numbers, maintenance of differences between groups for incidence and mortality may also suggest that stage at diagnosis and access to optimal treatments were perhaps equitable.

- A summary of patterns across indicators

Acknowledging data limitations, poorer stage of diagnosis, screening and treatment profiles for prostate cancer in farm men may have transferred to a slightly adverse effect on mortality, albeit not significantly. In particular, limited access may have led to the significant difference in brachytherapy utilisation by rural residents, especially farmers. This important differential may have contributed to the slightly elevated prostate cancer mortality outcomes of farm men in this cohort, not apparent for most other cancers.

In contrast, despite similar incidence and later stage, colorectal cancer mortality was considerably lower in farm men, though not significantly. Farm women had a similar colorectal cancer profile to men regarding incidence and mortality, although stage at diagnosis was similar to other groups. Breast cancer mortality risk was also lower in farm women than other residents - and significantly better than rural non-farm women, despite minimal differences in incidence and stage between groups. It has been suggested physical activity which was not controlled for in this study, may have impacted upon survival for these cancers, but the answers remain largely elusive.

In the absence of staging and treatment data on lung cancer, less than optimal treatment for farm and rural non-residents was alluded to by a relative gap closure or 'advantage gain' for urban residents against others, when comparing corresponding measures from incidence to mortality. Differences in melanoma and NHL, were generally maintained between incidence and mortality indicators, suggesting treatment options were not remarkably different.

Maintenance of relative group differences between incidence and mortality, controlling for common risk factors, suggests that the combined effects of stage at diagnosis and /or treatment on mortality risk, were likely to be similar for the two rural groups. In contrast, the gap between SIR / incidence hazard and SMR / mortality hazard for urban men closed or 'improved' relative to other

men. This suggests either earlier diagnosis or better access to specialist treatment for lung cancer in urban areas.

This discussion has attempted to explain the differences seen between groups in cancer indicators, from incidence through to mortality. Comparisons across several indicators can assist in identifying patterns that may have implications for rural health services and resource allocation. Most differences were not significant and case numbers were small. Suggested trends and inferences need to be confirmed with: (1) greater case numbers over longer periods of time; and (2) in other cohorts comparing farm, rural non-farm and urban residents.

9.4 Strengths and limitations of studies

There are a number of strengths of this research comparing cancer indicators between farm, rural non-farm and urban residents. The robust sampling methods of the original 45 and Up Study have resulted in enlistment of approximately one in ten residents aged over 45 years in NSW and a good representation of farm residents due to the oversampling in rural areas.

This study has also been able to identify and separate farm residents from rural non-farm residents to compare with urban residents - which has not been done in Australia and rarely done elsewhere in a cohort of this size. The ability to compare cancer indicators between resident groups of women has also addressed a lack of cancer indicators for women in occupationally defined studies of cancer in farmers.

The ability to link data to state and national health databases has been a significant advantage, capturing all health system interactions for a range of cancer-related services. Being able to compare indicators for the same cohort across the spectrum from cancer incidence, stage at diagnosis, screening, treatment and mortality, albeit at a group level, has also been an advantage not seen in other studies. Consequently, this study is unique with regards to the comprehensiveness of the

analyses undertaken. Due to the 45 and Up Study being an ongoing longitudinal study, it also provides the potential to repeat these analyses over a longer period of time, to re-assess findings.

There are also a number of limitations related to the study. Despite its large cohort size and the fact that it represented 16-17% of the population of NSW aged over 45 years at the time, this proportion means it cannot be claimed to be truly representative of the population of NSW. In addition, despite its large size, cancer events are rare, so numbers for some analyses were small, particularly within the farm resident cohort. This has resulted in low power for some analyses and wide confidence intervals, contributing to the lack of significance within the findings. The differences where case numbers are small, warrant conservative interpretation to avoid placing weight on point estimates with sometimes fluctuating and slightly unstable hazard or odds ratios.

Low numbers in the farm referent group also meant that caution needed to be taken with results for the less common cancers examined; especially when modelling and controlling for multiple risk factors. This meant that analyses including stage at diagnosis and treatments for lung cancer, NHL and melanoma could not be undertaken with confidence; and therefore were not.

The above limitations related to low numbers and wide confidence intervals are largely a consequence of limited follow-up time for events to occur since recruitment into the study. A longer follow-up period would also incorporate possible changes in cancer indicators that may have occurred since the significant investment in rural cancer services in New South Wales that has occurred over the past 5 years.

The farm cohort for this study was defined by residence, but not all farm residents are occupational farmers - and not all occupational farmers are farm residents. Whilst it has been described that the majority of farmers are indeed farm residents, the lifestyle and exposures of recreational versus occupational farmers will blend along a continuum.^{1, 38-39} This may have affected

both the representativeness of sub-groups and internal validity of comparisons made. However, classification of residence is independent of other risk factors that affect cancer outcomes, so errors arising from misclassification are likely to be non-differential. This would tend to cause a bias toward the null and underestimation of any relationship between farm residence and the cancer outcome measured. Lastly, the definition of farm, rural non-farm and urban residents was based on the 45 and Up Study baseline questionnaire. Residential status and risk factors are not necessarily static and the status of these may have changed over time, again likely to weaken potential differences between resident groups.

The quality of data also varied by variable and by dataset. Measures have been taken to minimise data entry errors, but a proportion will remain. Also, self-report survey data is sometimes regarded as less robust than administrative population-wide data, although some studies have reported relatively good correspondence between self-report and administrative health data for this cohort;⁴⁰ and for self-reported 'intention to screen' data elsewhere.⁴¹⁻⁴² Other dataset quality issues include the large proportion of unrecorded stage in the NSW CR for prostate cancer cases;⁴³ leading to lower confidence in results for prostate cancer.

There was also the likelihood that not all mammograms, PSA tests, FOBTs or colonoscopies in the MBS were purely for screening purposes, because similar tests are used with symptomatic persons. It is not known if this is independent of residential classification or not, but it does potentially affect the validity of measures used to assess screening differences. Relatively poor capture of chemotherapy and radiotherapy treatments for Cancer Registry defined cases in the APDC were reported by some authors;⁴⁴⁻⁴⁵ although cancer cases were identified differently in the current study using APDC admission diagnoses fields. Nonetheless, these studies suggest there is the potential for a positive bias toward higher odds of prostate cancer therapies amongst

urban men.⁴⁴⁻⁴⁵ In summary, data quality limitations as detailed for each analyses, should be taken into consideration when interpreting results.

For analyses with a larger number of variables included in the base models, collinearity may have been present to some degree, even though checks were undertaken to ensure this was not excessive. This study has also undertaken multiple comparisons and analyses of the 45 and Up cohort. Statistically, a proportion of analyses will produce significant results due to each analysis being a member of a population of analyses, to produce false positive results. However, this problem is more of a concern where multiple analyses are conducted simultaneously - or in comparing multiple groups.⁴⁶ In this study, only three sub-groups were compared, with the number of possible outcomes being dichotomous or minimal. Additionally, analyses generally progressed longitudinally and were often conditional, rather than being independent and simultaneous as required by the assumptions of Bonferroni and other correction procedures.⁴⁷

Lastly, this study progressing from incidence, staging, screening, treatment and possible mortality of the selected cancer, has been a comparison of group indicators. In reality this progression is an individual journey.

9.5 Implications for health services and for further research

This study has generally found that farm residents had more favourable all cancer incidence and mortality profiles than rural non-farm or urban residents, but most differences between groups were not significant and there is a need to assess these trends over a longer period of follow-up time. However, if confirmed in other studies over longer periods of time, there are differences that warrant further investigation.

Firstly, there is more to learn about the prostate cancer profile in farm men. Data limitations aside, if incidence, screening and odds of non-surgical treatments are truly similar between the two

rural groups, why did farm men have more prostatectomies - and why was mortality higher in farm men? Do farm men have more aggressive forms of prostate cancer that may have been evident if more cases had recorded stage? In addition, compared to urban men, is the significantly lower utilization of brachytherapy and chemotherapy in both rural groups due to inadequate access?

For breast cancer, farm women had mildly lower incidence, but considerably lower mortality. Longer follow-up time to assess incidence data would confirm if farm women in this cohort actually do have the lower incidence rates suggested in this study. If so, why might this be the case? Do certain lifestyle features of living on a farm lower the risk of breast cancer incidence? We have proposed that perhaps greater physical activity and exposure to sunshine may be contributing factors. However, other factors not assessed in this study may also make a difference, such as education levels, self-employment and sense of control; or perhaps fresh fruit and vegetable consumption.

Why do farm women have such better mortality outcomes than other women for breast cancer, significantly better than rural non-farm women? Is this related to potentially lower incidence and earlier stage at diagnosis? And why do farm women have better mortality outcomes with seemingly less chemotherapy? Is this also related to earlier stage at diagnosis, such that chemotherapy is less likely to be required? It is unlikely to be related to lower health service access, because farm women had less chemotherapy than rural non-farm women, yet more favourable mortality outcomes. Again, these trends need to be confirmed over a longer period of follow-up. This would determine if the significant investment in rural cancer services in NSW in recent years has made a difference to rural cancer indicators. The role of screening, which did not appear to be better in farm women in our data, could also be investigated further, particularly in relation to the role of promotion campaigns previously conducted by rural community organisations.

For colorectal cancer, there seemed to be little difference in cancer incidence for men or women, but whilst not significant, farm residents had considerably better mortality than other groups. Again, if putting data limitations aside, questions arise as to why farm men are more likely to be diagnosed at later stage. In addition, if both farm and rural non-farm residents have less optimal colorectal cancer treatments than urban counterparts, why did farm residents have much lower rates of mortality? These questions have implications for health services and colorectal cancer care in rural areas.

For other cancers, lower incidence and mortality were generally suggested in farm residents, particularly lung cancer incidence in farm women. This had been found elsewhere with exposure to endotoxins on farm a suggested explanation.⁴⁸⁻⁵⁰ Longer follow-up would confirm the trend for this cohort, as small numbers were a limitation. However, there is also potential to confirm whether on-farm exposures are associated with reduced incidence in this cohort; which would be a significant sub-study. Findings may have ramifications for immunological research into the future for protecting against the development of lung cancer.

For melanoma, there is also the potential for further exploring how moderate-level occupational sun exposure might be less harmful and protective against melanoma, compared to intermittent intense recreational sun exposure. This might be achieved by confirming trends shown in this study; or by a more detailed sub-study on sun exposure patterns. Results in this study for NHL were largely inconclusive, likely related to low numbers. Again, further follow-up may reveal whether cancer indicators vary between farm, rural non-farm and urban residents.

Amongst the many questions raised that could be investigated further, there are three avenues that are the most important or potentially efficient in solving unanswered questions and meeting unmet needs. These are:

1. The need to confirm the trends suggested in this cohort over a longer period of follow-up that encompasses data since more recent investment in rural cancer services; and by investigating other cohorts. If findings of the current research are confirmed:
2. There is a need to address health service-related factors regarding:
 - higher risk of later stage diagnosis of colorectal cancer in farm men
 - lower rates of brachytherapy, chemotherapy and combined therapies for prostate cancer in farm men
 - ongoing attention to wider rural disadvantage in non-surgical cancer treatments for prostate, colorectal and breast cancers; and perhaps lung cancer.
3. Further investigation of the possible reasons why farm residents have generally better incidence and / or mortality profiles for breast, colorectal and lung cancers; that might inform ways to reduce the impact of these cancers upon individuals and wider communities. In particular, this might include investigation of:
 - lower lung cancer rates and possible farm exposures - particularly on dairy farms, where international studies have suggested links with endotoxin exposures⁴⁸⁻⁵⁰
 - lower breast cancer in farm women - the possible roles of physical activity and sun exposure
 - lower colorectal cancer in farm residents - the possible roles of physical activity and diet.

Addressing these questions will contribute to a greater understanding of the epidemiology of cancer in Australian farm residents.

9.6 References

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