ECONOMIC ESSAYS ON BURDEN, SURVIVORSHIP AND HEALTH LITERACY – A FOCUS ON HPV-RELATED HEAD AND NECK CANCER

A THESIS SUBMITTED FOR

THE DEGREE OF DOCTOR OF PHILOSOPHY

FROM

DISCIPLINE OF ECONOMICS,

J.E. CAIRNES SCHOOL OF BUSINESS AND ECONOMICS

AT

THE NATIONAL UNIVERSITY OF IRELAND, GALWAY

BY

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September 2014

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Declaration

I declare that this thesis, submitted to the National University of Ireland, Galway for the degree of Doctor of Philosophy (Ph.D.) has not been previously submitted as an exercise for a degree at this or any other University. All research herein is entirely my own.

Signature: Date:

Abstract

Our understanding of cancer and the role of specific agents in its cause continues to evolve. Head and Neck Cancers (HNC) in the developed world were traditionally associated with excessive smoking and drinking. Since 2000, the Human Papilloma Virus (HPV) has been linked with a subset of HNC in the oropharynx region and the prevalence of these has increased markedly among males aged 40-65 years of age. As with any emerging epidemic it is important to gain an understanding of the causes and effects to help inform a policy response. In this thesis, I examine issues around the characterisation of disease burden; cancer survivorship and health literacy supported by a range of empirical analyses to help provide insights into the development of a policy response to HPV-related HNC

In characterising the economic burden of HPV-related HNC in the United States, the absence of a consensus on or accepted guidelines for Cost-of-illness (COI) studies has seen a range of methods deployed in the literature. Four commonly used approaches to estimating the direct medical expenditures on HNC using the Medical Expenditure Panel Survey (MEPS) highlight the impact choice of method has on characterising disease burden. The range of average annual (2003-2008) direct medical expenditures for adults with HNC in the US was $754 million to $3.18billion; variations in confidence intervals around estimates are evident. The range underscores the importance of adopting robust approaches to burden estimation if the urgency of a policy response is to be accurately communicated.

As HPV-related HNC has a good prognosis, clinical trials are focused on deintensification of treatment with the view of improving the quality of life of survivors. These facts prompted an examination of service use among cancer survivors. The thesis examines healthcare utilisation of

cancer survivors in general in Ireland using The Irish Longitudinal Study of Ageing (TILDA). Count and bivariate probit regression analyses are used to estimate the relationships between service utilisation among cancer survivors relative to those with no history of diagnosed cancer, controlling for a range of covariates. Emphasis is given to the role of time since diagnosis among cancer survivors to highlight how the impact of cancer on service utilisation varies as survivors move from active treatment to what might be called the survival phase. The implications of this in planning services for highly survivable cancers such as HPV-related HNC are explored.

Communication will be central to any policy response to an emerging epidemic. The absence of a health literate population has the potential to compromise the effectiveness of any policy response. An examination of health literacy, as a public health or health inequality issue is examined within an Irish context to ascertain how literacy might best be enhanced as a precursor to policies aimed at addressing HPV-related cancer. The empirical analysis demonstrates that Irish policy-makers ought to take a public health (rather than a health inequalities) perspective in respect of health literacy.

Finally, policy recommendations are proffered informed by the analyses undertaken to address the emerging epidemic of HPV-related HNC. These recommendations emphasise the importance of a broad multidisciplinary response.

Acknowledgements

"All The Pieces Matter"

Detective Lester Freamon (Character from 'The Wire' TV series set in Baltimore, Maryland)

Doing a PhD is a lot like doing a marathon. It requires discipline, commitment and a lot of persistence! What makes doing a PhD and a marathon easier is the support of mentors, colleagues, family and friends. To begin with, I'd like to acknowledge and thank the All-Ireland Cancer Consortium, the Health Research Board and the National Cancer Institute for creating the Health Economics in Cancer Prevention Fellowship. I was delighted to be selected by an expert interview committee for this prestigious Fellowship (albeit on my second attempt!). This was a wonderful opportunity, which allowed me to study at Johns Hopkins School of Public Health (JHSPH) and for that, I will be forever grateful.

From the moment I arrived in Baltimore (July 2010), I was made feel very welcomed by the Department of Health Policy & Management at JHSPH. Professor Kevin Frick is a tremendous mentor and friend. He opened many doors for me to ensure that I had very enriching experience in America. Words fail my appreciation. One of those early meetings was with Dr. Christine Gourin from the Johns Hopkins Medical Institution (JHMI) who introduced me to HPV-related Head and Neck Cancer world. As a Fellow in Cancer Prevention, I felt that this subject matter fitted my remit. I'd especially like to thank Professors William Westra and Sara Pai (JHMI) for all their help in securing data and projects for me to work on. Finally, I'd like to thank my colleagues at JHSPH - Susan Yeh, Christine Buttroff and Giselle Gallegos for all their support, encouragement and friendship. I'd also like to thank the Baltimore GAA and the Hopkins Marathon Team for keeping me sane throughout this time in my life.

I was delighted to continue working on Health Literacy in Baltimore. I like to thank Professor Antonio Trujillo for helping me the empirical analysis. I'd also like to thank the health literacy community in the UK and North America especially Gillian Rowlands, Deborah Begoray and Doris Gillis who were the editors of the book - Health Literacy in Context: International Perspectives.

When I returned to NUI Galway in July 2012, I was delighted to be joining a vibrant health economics department. I'd like to thank all the staff and students in the Department of Economics for their help and kindness especially Brendan Kennelly as head of the discipline. My main supervisor throughout the PhD process has been Professor Ciaran O'Neill. Since we first met in 2009, he has been very patient and supportive of my endeavours. He has guided me through the last 5 years of this learning process and I am indebted to his professionalism, intelligence and caring nature.

My friends Niamh Quinn, Sharon Commins, Ollie Halley, Dave O'Riordan and Pat Dooher, were great to me. Thanks also to the Joe Higgins PhD room - Joshua Curis, Tanja Florath, Helen McDermott, Herath, Daniel Higgins, Riad Cheikh-el-Ghanana and Gabriela Gilga for their warmth and conversation. The Health Economics team in Galway were also great colleagues. Sincere thanks to Trish Carney, Michelle Queally, Aine Roddy, Richeal Burns, Brendan Walsh, Andrii Danyia, Stephen O'Neill, John Cullinan, Aoife Callan, Paddy Gillespie and Edel Doherty. Special mention to my dear friend, – Padraic Ward for being a 'good lad' and a stata guru!

I'd like to thank my family - My parents Tommy and Mary, my brother Thomas and my sisters Sinead and Elaine for their love and support. Special mention must go to the 'Purtills' (Sinead, Bobby, Aoife and Niamhie) in Glasson where I could go for a warm meal and plenty of laughter. Finally, thanks to Damien McKeon for his inspiring pep-talks.

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List of Abbreviations and Acronym

AIC – Aikake Information Criteria

ACS – American Cancer Society (US)

ADL – Activities of Daily Living

AHRQ – Agency for Healthcare Research and Quality (US)

APC – Annual Percentage Change

ASCO – American Society of Clinical Oncology

ASIR – Age Standardised Incidence Ratio

BIC – Bayesian Information Criteria

CAPI – Computer-Assisted Personal Interview

CCI – Charlson Comorbidity Index

CCS – Clinical Classification Software (MEPS)

CDC – Centres for Disease Prevention and Control (US)

CEA – Cost-Effectiveness Analysis

CI – Confidence Interval

CI – Concentration Index

CMS – Centers for Medicare & Medicaid (US)

COI – Cost-of-illness

CRD – Centre for Review and Dissemination

CSO – Central Statistics Office (IRL)

DED – District Electoral Division (IRL)

EBV – Epstein-Barr Virus

EED – Economic Evaluation Database

EEE – Extended Estimating Equations

EU-HLS – European Union Health Literacy Survey

FDA – Food and Drug Administration (US)

FMM – Finite Mixture Model

FNA – Fine Needle Aspiration

GBMC – Greater Baltimore Medical Centre

GGM – Generalized Gamma Model

GLM – Generalized Linear Model

GMS – General Medical Services (IRL)

GP – General Practitioners (IRL/UK)

HC – Household Component (MEPS)

HC-2 – Hybrid Capture 2 Assay

HCUP – Health Care Utilisation Project (US)

HES – Hospital Episode Statistics

HESG – Health Economics Study Group

HINTS – Health Information and Trends Survey

HIPE – Hospital In-Patient Episodes

HLM – Health Literacy Missouri (US)

HNC - Head and Neck Cancer

HNSCC – Head and Neck Squamous Cell Carcinoma

HPV - Human Papilloma Virus

HR – Hazard Ratio

HTA – Health Technology Assessment

IADL – Instrumental Activities of Daily Living

IARC - International Agency on Cancer Research

IC – Insurance Component (MEPS)

ICD – International Classification of Diseases

ICD-O-3 – International Classification of Disease Oncology Version 3

ICD-9-CM – International Classification of Diseases, Ninth Revision, Clinical Modifications

IMRT – Intensity Modulated Radiation Therapy

IOM – Institute of Medicine

IRR – Incidence Rate Ratio

ISPOR – International Society of Pharmacoeconomics and Outcomes Research

ISRCTN – International Standard Randomized Controlled Trial Number

JHMI – Johns Hopkins Medical Institute (US)

JHSPH – Johns Hopkins School of Public Health

KEDS – Knowledge Exchange and Dissemination Scheme

LC – Latent Class

LR – Likelihood Ratio

MAE – Mean Absolute Error

MAPE – Mean Absolute Prediction Error

MEPS – Medical Expenditure Panel Survey (US)

MeSH – Medical Sub Headings

MPC – Medical Provider Component (MEPS)

MSA – Metropolitan Statistical Area

MSM- Men who have Sex with Men

NB – Negative Binomial

NCCN – National Comprehensive Cancer Network (US)

NCCP – National Cancer Control Programme (IRL)

NCHS – National Centre of Health Services (US)

NCRI – National Cancer Registry Ireland (IRL)

NHANES – National Health and Nutrition Examination Survey (US)

NHIS – National Health Interview Survey

NHS – National Health Service (UK)

OLS – Ordinary Least Squares

ONS – Office of National Statistics (UK)

OLS – Oral Lichen Planus

OP - Outpatient

OPC – Oropharyngeal Carcinoma

OPSCC – Oropharyngeal Squamous Cell Carcinoma

OR – Odds Ratio

OSCC – Oral Squamous Cell Carcinoma

PCP – Primary Care Physicians (US)

PPO – Preferred Provider Organization

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta Analysis

PSM – Propensity Score Matching

PUF – Public Use Files

PYLL – Potential Years of Life Lost

PVFLE – Present Value of Future Lifetime Earnings

PVLE – Present Value of Lifetime Earnings

QALY – Quality Adjusted Life Year

QoL – Quality of Life

QPC – Quality Priority Conditions (MEPS)

RESET – Regression Equation Specification Error Test

RMSE – Root Mean Square Error

SAH – Self-Assessed Health

SAMH – Self-Assessed Mental Health

SCCHN – Squamous Cell Carcinoma of the Head and Neck

SCP – Survivorship Care Plan

SEER – Surveillance Epidemiology and End Results

SLAN – Survey of Lifestyle Attitude and Nutrition

SMDM – Society of Medical Decision Making

SRR – Standardised Risk Ratio

SUNB – Seemingly Unrelated Negative Binomial

SUP – Seemingly Unrelated Poisson

TES – Transoral Endoscopic Surgery

TILDA – The Irish Longitudinal Survey on Ageing

TORS – Trans Oral Robotic Surgery

USPSTF – United States Preventative Service Task Force

YPLL – Years of Potential Life Lost

WHO – World Health Organisation

UN – United Nations

ZINB – Zero Inflated Negative Binomial

ZIP – Zero Inflated Poisson

Chapter 1: General Introduction and Background

Our understanding of the causes and effects of cancer continues to evolve. In his Nobel prize lecture in 2008, Professor Harold zur Hausen, the German virologist who discovered the role of HPV in cervical cancer, estimated that 20% of all cases of human cancer are now aetiologically linked to viral infections (Zur Hausen, 2009). The 2008 World Cancer Report estimated that 550,000 or 6.1% of worldwide cancer cases are attributable to the Human Papilloma Virus (HPV) – the most carcinogenic virus followed by Helicobacter pylori (5.4%) and Hepatitis B & C virus (4.3%) (Thun et al., 2010). In 2013, the influential US Annual Report to the Nation on the Status of Cancer (Jamel et al. 2013) specifically reported on the increase in HPV-related cancers, especially those involving the oropharynx, and the low levels of HPV vaccination coverage in the US.

The linkage of HPV to the head and neck region presents both a challenge and opportunity to policymakers, particularly in the developed world. The age and gender profile of HPV-related HNC is different to that of many other cancers, affecting predominately younger (40-65 years) men whose interaction with health services may differ to that of other groups. Similarly, post-treatment survival of HPV-related HNC is higher than for many other cancers making late treatment effects and long-term surveillance perhaps more important than with other cancers. That there also exists the potential to extend preventive cancer control programmes such as HPV vaccination also makes it somewhat different to other cancers.

The potential for the discipline of health economics to contribute to contemporary understanding of the effects and management of the disease is considerable. In this thesis, three particular themes are examined: the characterisation of disease burden and the methods by

which this is done; an examination of the level of healthcare utilisation during the survivorship phase among cancer patients and the role of context in understanding this phase; and an exploration of the importance of health literacy in communication around cancer as part of an effective cancer control strategy.

1.1 Motivation: Emerging Epidemic and Economic Methodology

The overarching motivation of this thesis stems from the reality that the role of causal agents in the burden of cancer is changing. The fact that HPV causes cancer in a number of anatomical sites other than cervical cancer has only been discovered in the last fifteen years. That incident cases of HPV-related HNC will surpass cervical cancer by 2020 and that HPV-related HNC is predominately seen in men has only recently come to be appreciated (Chaturvedi et al., 2008). Policy-makers, healthcare professionals and the general public need to be made aware of these facts to act appropriately to lessen the likelihood of negative outcomes with this (potentially) modifiable cancer. Currently, policy-makers in developed countries are faced with choices regarding gender-neutral HPV vaccination. Since February 2013, the HPV vaccine is being provided free in schools in Australia to boys as part of their National Immunisation Program (Wilkinson, 2012). Other countries may choose to follow suit.

In the development of effective cancer control strategies, it is often necessary to describe the issue using metrics that are widely understood in order to provoke a policy response. Describing the burden of a disease in monetary terms is one such method. A variety of approaches exist, however, by which estimates of the cost-of-illness (COI) may be generated (Rice, 1994). This thesis investigates the methods of estimating the 'direct medical expenditure' using the Medical Expenditure Panel Survey (MEPS) and the differences that can arise from them using HNC as a specific empirical example. This work draws on a seminal review that, identified four distinct estimation methods (Akobundu et al., 2006) and discusses the implications of the findings.

As HPV-related HNC has high cure rates (~95% 3-year survival), minimising the long-term effects of treatment is an important issue for

treating oncologists. With the increase of cancer survivors, the field of cancer survivorship has expanded. In Ireland, however, there is a paucity of research in this area. Given the unique features (e.g. public and private healthcare financing mix) of the Irish healthcare system, it is difficult to extrapolate from other contexts what the pattern of service use might resemble among cancer survivors relative to those with no history of diagnosed cancer here. This thesis compares the level of service use among cancer survivors with those who have not had a cancer diagnosis using a population-based survey of the over-50s (TILDA) in Ireland. A number of count based and bivariate probit models are used to examine the impact of cancer on the level of service use and how this changes as the length of time from diagnosis increases.

Finally, the importance of cancer communication in cancer prevention has received relatively little attention from health economists. A basic determinant of health and cancer prevention is health literacy. As the burden of HPV-related HNC emerges, greater consideration ought to be given by policy-makers on raising awareness and understanding of the disease. Fundamental to that challenge is the concept of health literacy. This thesis examines the demand for a health literate healthcare system across the socioeconomic groups in Ireland using a population-based survey {the Survey of Lifestyle, Attitudes and Nutrition (SLAN)}. Starting with logistic regression analysis, the analysis extends to include an estimation of income-inequality related concentration curves and indices. The analysis is used to support the adoption of a public health as opposed to a health inequalities response to health literacy and by extension cancer communication in Ireland.

1.2 Aims and Objectives of the Thesis

The overall aim of the thesis is to explore healthcare utilisation with respect to cancer and the role of health literacy in understanding this. Three specific objectives are addressed: How should economists characterise the burden of illness and specifically the burden of illness related to HNC; what is the pattern of healthcare utilisation of cancer survivors in Ireland and how does that pattern change with time since diagnosis and; what role could health literacy play in cancer communication strategies. The thesis is set within a context of an emerging HPV-related HNC epidemic and the clinical and public health issues related to this type of cancer are used to illustrate the broader themes explored in the thesis.

The first objective relates to the impact different methods of estimating the direct medical expenditures associated with an illness, in particular HNC, has on the magnitude of the cost estimate derived. The objective is to compare and contrast the different approaches to the estimation of direct medical expenditures associated with HNC in the US using the MEPS dataset. MEPS collect information (from source) of disease-specific medical expenditures and therefore suitable for the intended study design of comparing approaches to estimation in deriving a national estimate of the burden of a disease. A limitation of the empirical example selected is the small sample size available. This is both a challenge and a strength of the thesis in that the specific example selected serves to underscore the impact of method on what is a relatively rare cancer with limited sample heterogeneity. The use of MEPS data is deliberate in that this is a dataset used by many to make national estimates of the economic burden of a disease

As over 90% of those with HPV-related HNC go on to be cancer survivors, the research question regarding how best to manage their follow-up care becomes pertinent. As more people survive cancer, the demand for services will increase. In the empirical analysis, the specific objective is to examine the level of healthcare utilisation among cancer survivors in Ireland relative to those without a history of cancer using the TILDA dataset and how this varies with time since diagnosis and type of cancer. TILDA allows for this by virtue of an in-depth self-reported section on healthcare utilisation by respondents in the previous 12 months. Although the level of detail regarding the nature of the contact with the healthcare system is lacking, the importance of this analysis is that it is the first time that the healthcare use of people with a history of cancer in Ireland has been scrutinised and its implications for policy explored within an evidenced based context.

The health literacy theme explores the research question of whether health literacy policy should predominately be a public health or health inequalities issue in Ireland. In the empirical analysis, the specific objective is to test whether a socioeconomic gradient in the demand for a health literate healthcare system exists, by using pooled data from the SLAN data sets. These data sets are suitable as they allow for the construction of a demand for a health literate healthcare system variable. Despite using historic data sets, this novel approach has significance to the literature in that it is the first analysis of a survey that gives insight into the difficulty those users has with engaging and accessing the healthcare system in Ireland.

1.3 Thesis Outputs

There have been a number of outputs from the research undertaken for this thesis to date, details of which are listed below for information. These include three first-author peer-reviewed published articles (and one under review), two editorials, one chapter in an international book as well as a contribution to a study on HPV diagnostic testing in HNC. The research has also been presented at a number of conferences and seminars in Ireland and internationally, and these are also listed. Another contribution was the organisation of a symposium as part of a Knowledge Exchange and Dissemination Scheme (KEDS) grant on HPV-related HNC in Galway in May 2013.

First-Author Papers

- Coughlan D., Yeh S., O'Neill C. & Frick KD. 2014. Evaluating direct medical expenditures of a condition using Cost-of-Illness (COI) methodology as applied to the Medical Expenditure Panel Survey (MEPS): The case of Head and Neck Cancer. *Value in Health*; 17(1): 90-7
- Coughlan D., Turner B. & Trujillo A. 2013. Motivation for a health literate healthcare system – Does socioeconomic status play a substantial role? Implications for an Irish health policy-maker. *Journal of Health Communication*, 18: 158-171
- Coughlan D., O'Connor T. & Keogh IJ. 2013. The Jade Goody legacy has undoubtedly saved lives, but what will be the Michael Douglas effect? *Irish Medical Journal*, 106(7): 197
- Coughlan D., O'Connor T., O'Neill C., Frick KD., Westra WH., Pai SI., Keogh IJ. 2013. Oncopolicy in high-income countries can make a difference in HPV-related Head and Neck Cancer. *Journal of Cancer Policy*, 1(3-4): e49-51

- Coughlan D. & Frick KD. 2012. Economic Impact of HPV-Related Head & Neck Cancers in the US. *Otolaryngologic Clinics of North America*, 45(4): 899-917

Contribution

- Smith DF., Maleki Z., Gooi Z., Coughlan D., Akpeng B., Ogawa T., Bishop J., Frick KD., Agrawal N., Gourin CG., Ha P., Koch W., Richmon JD., Westra WH., Pai SI. 2014 Human Papillomavirus status of Head and Neck Cancer as determined in cytologic specimens using Hybrid-Capture 2 assay. *Oral Oncology*, 50(6): 600-4

- Saber-Tehrani A., Coughlan D., Hsiang YH., Korley, F.,Mantokoudis G., Frick KD, Newman-Toker, D. 2013. Rising annual costs of dizziness presentations to US emergency departments. *Academic Emergency Medicine*, 20(7): 689-96

- O'Neill C. & Coughlan D. 2011. Importance of Adherence and the Role of Nonfinancial Barriers. *Clinical Therapeutics,* 33:9: 1222-4

Under Review

- Coughlan D. Doherty E. Ward P. Frick KD. O'Neill C. Healthcare utilisation of cancer survivors' over-50yrs of age in Ireland: Findings from a population-based survey (*Journal of Cancer Survivorship – submitted January 2014)*

Book Chapter

- Coughlan D. Health Literacy: An Economic Perspective. Chapter published in book entitled: Health Literacy in Context: International Perspectives. 2012. Nova. New Jersey.

Oral Presentations

- 54th Annual Conference of the Irish Otorhinolaryngology Society 2013; October 11-12th. Ashford Castle, Cong, Co. Mayo. Topic: HPV and Head and Neck cancer – New cancer epidemic? Clinical and public policy updates

- Health Economics Study Group (HESG) 2010; June 23-25th. University College Cork. Topic: Health Literacy – An Economic Perspective to a Measureless Concept

- Health Literacy – Making the Most out of Health (London South Bank University, February 24th 2010) Topic: Health Literacy: An Economic Perspective

Poster Presentations

15th European ISPOR Conference 2013; November 2-6th. Dublin, Ireland

- PHP215: Clinical, epidemiological and economic metrics differences between HPV-related and traditional Head and Neck Cancers

14th European ISPOR Conference 2012; November 3-7th. Berlin, Germany

- PCP200: Effective demand for a health literate healthcare system: Evidence from Irish survey data

17th Annual ISPOR Conference 2012; June 2- 6th. Washington DC, USA

- PCN150: Direct medical costs of head and neck cancer in the united states: an analysis using pooled medical expenditure panel survey (MEPS) data

- PRM54: A conceptual analysis of when medical expenditure panel survey (MEPS) meets cost of illness (COI) – Are they a match?

2nd Health Literacy Annual Research Conference 2010; October 18-19th. Bethesda, Maryland, USA

- Health Literacy: The various economic angles to a measureless concept, implications for the National Health Service (NHS) in England

Symposium Organiser

May 17th 2013 – National University of Ireland, Galway

- HPV and Head and Neck Cancer - New Cancer Epidemic? Clinical and Public Policy Updates from International Experts

http://www.conference.ie/Conferences/index.asp?Conference=200 (Last accessed: 16th April 2014)

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Zur Hausen, H., 2009. The search for infectious causes of human cancers: where and why. *Virology,* 392, 1–10.

Chapter 2: Head and Neck Cancer and the Human Papilloma Virus Link

Economics is the study of choice and there are various decisions to be made along the cancer care pathway. The discovery of the link between HPV and HNC is a significant development that is likely to impact upon decision-makers at various levels. In 2000, a paper published by a group of clinical academics from Johns Hopkins Medical Institution (JHMI) implicated HPV as a factor in a subset of cancers found in the Head and Neck region (Gillison et al., 2000). By 2007, the International Agency for Research in Cancer (IARC) had sufficient evidence to declare HPV as a causal agent for cancers in the oropharynx (IARC, 2007). Further, in the summer of 2013, the Hollywood actor, Michael Douglas, received significant media attention by linking oral HPV transmission to HNC through sexual activity. Each of these three events (Figure 1) can be viewed as being 'game-changing' moments – The initial discovery has led to pioneering academic research across the globe, IARC's monograph has influenced clinical practice and Michael Douglas's comments exponentially increased public awareness and expedited the public health response.

Figure 1: Timeline of HPV and Head and Neck Cancer

This thesis employs an economic perspective to contextualise care treatment pathway options for HPV-related HNC by focusing on the broad themes of measuring burden, exploring healthcare utilisation in survivorship and promoting health literacy with specific reference to this emerging virus-induced cancer. This chapter first provides context to the discussion that follows by outlining the anatomic site of the cancer, the virus, the known epidemiology and the current treatment options. This brief introduction will highlight HPV-related HNC as a distinct molecular, clinical and epidemiological entity (Gillison, 2004), distinct from traditional HNCs. Some pertinent nuances will be elaborated upon to emphasise that this type of cancer also has a distinct economic profile. These features are important for policy-making and are addressed in the subsequent empirical research that characterises the economic burden of this new disease, the impact on healthcare utilisation and on cancer communication.

2.1 Head and Neck Cancer

Cancers of the head and neck region are a heterogeneous group (17 sites) of neoplasms that share a common anatomic origin. These cancers are described according to the type of cell the cancer started in. The most common type of HNC is squamous cell carcinoma (HNSCC).[1] These are the skin cells lining the mouth, nose and throat. Indeed, HNSCC accounts for 90% of all HNC and these are the cancers associated with HPV. Cancers of the head and neck are further categorised by the area of the head or neck in which they begin. The areas affected and are labelled in Figure 2 (NCI, 2013).

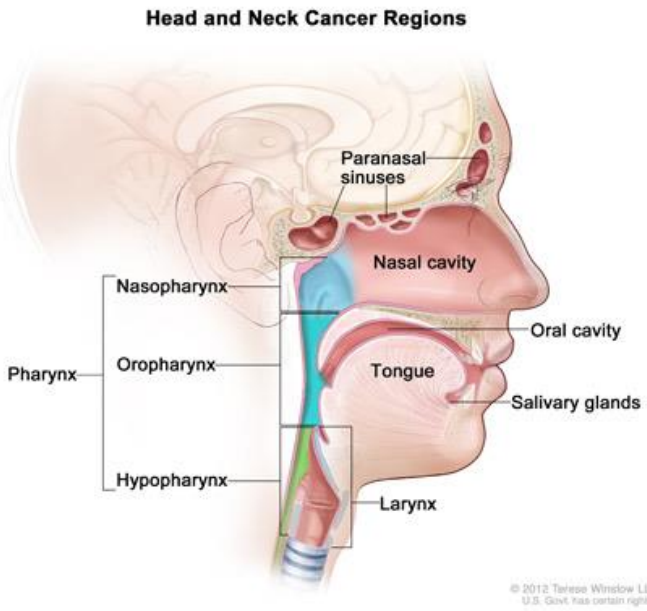

Figure 2: Sites of Head and Neck Cancers (NCI 2013)

It should be noted that cancers of the brain, the eye, the oesophagus, and the thyroid gland, as well as those of the scalp, skin, muscles, and bones of the head and neck, are not usually classified as HNCs (NCI, 2013).

[1] The other cancer types are derived from lymphomas (white blood cells), adenocarcinomas (cells that line the glands in the body) and sarcomas (develop from the cells that make up muscles, cartilage, bone or blood vessels) (Macmillan 2012).

Causes of Head and Neck Cancer

Accurately identifying the causal agents shapes the cancer control policy response. Ireland has made huge strides in combating smoking through increasing taxes on tobacco products, banning smoking in the workplace and maintaining a high-intensity media campaign (Currie et al., 2013). The same however can not be said about alcohol policy (Murphy, 2012). Most HNSCCs in the industrialised world have traditionally been caused by excessive tobacco and alcohol use. The sites predominately affected are the oral cavity, larynx and hypopharynx (Sturgis and Cinciripini, 2007). Individuals afflicted by smoking or drinking-related HNC often have poor underlying health status, which contributes to their poor survival rates. In India, chewing betel (arcea) nut is a primary cause for the high number of cases (~75,000/per annum) of oral cancer. [2] The Epstein-Barr Virus (EBV) is also strongly associated with nasopharyngeal cancer (Wentzensen and von Knebel Doeberitz, 2004).

The primary focus of clinicians treating HPV-related HNSCC is in the oropharynx, as the virus has an affinity for the lymphoepithelium of the Waldeyer ring. These oropharyngeal squamous cell carcinomas (OPSCC) include the tonsils and base of tongue.

For the reminder of the thesis, HPV-related HNC is the broad term that will be used instead of the clinical precise definition of HNSCC and OPSCC.

[2] The highest prevalence of oral cancer in the world is in India and this number is increasing (Gupta et al., 2013). Infact, 86% of global oral cancer incidence is in India Source: http://www.deccanherald.com/content/309608/86-per-cent-global-oral.html (accessed 4th April 2014. In comparison with the U.S. population, where oral cavity cancer represents only about 3% of malignancies, it accounts for over 30% of all cancers in India
Source:http://www.nypcancerprevention.com/archive_newsletter/issue/14/cancer_prevention/feature/india.shtml(accessed 4th April 2014)

2.2 Human Papilloma Viruses

According to the IARC monograph on carcinogenic agents: *"Papillomaviruses are small, non-enveloped, epitheliotropic, double-stranded DNA viruses that infect mucosal and cutaneous epithelia in a wide variety of higher vertebrates in a species-specific manner and induce cellular proliferation"* (IARC, 2007). HPV is the most commonly sexually transmitted infection. Up to 75% of sexually active people in the United States will have HPV at some time in their lives (Satterwhite et al., 2013). Intimate sexual contact is the established route of transmission and viral persistence can lead to clinical issues such as genital warts and cancer.

Over 100 different subtypes of HPV have now been identified, distinguished by variations in their genetic sequence (Muñoz et al., 2003). Some types, such as HPV-6 and HPV-11 are known as 'low-risk' subtypes that cause genital warts. Other types, HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and 73 are known as 'high-risk' subtypes as they can cause cancer (Muñoz et al., 2003). The most commonly known site of HPV-related cancer is a woman's cervix. However, HPV can cause cancer in other anogenital sites – vulva, vagina, penis and anus (more in chapter 2).

Many HPV infections in the oral cavity (i.e. oral HPV infection) are cleared by the immune system (Peitsaro et al., 2002). The clinical literature has shown the importance of a functioning immune system in controlling HPV infection and its associated cancers.[3] Foremost is the observation that most immune-competent individuals infected with HPV are able to clear the infection without any clinical manifestation, and only 10% of infected individuals develop HPV-related lesions (Giuliano et al., 2011a).

[3] Immunocompromised individuals such as organ transplant recipients' on immunosuppressive medications (Paternoster et al., 2008) and patients infected with human immunodeficiency virus (HIV)(D'Souza et al., 2007a) have been documented to have significantly increased rates of HPV infections and HPV-related diseases (Tebeu et al., 2006).

2.3 Risk Factors of HPV-related Head and Neck Cancer

Epidemiologic studies show that there are several notable differences in the demographics of patients who develop HPV-related HNC compared with HPV-unrelated HNC patients. Patients who have HPV-related HNC are on average younger, more likely to have a higher socioeconomic status, higher educational attainment and more likely to have multiple lifetime sexual partners (Gillison et al., 2008)(Benard et al., 2008). In the US, it has been noted, not without controversy, that being white is also associated with higher incidence of HPV-related HNC (Benard et al., 2008).

The increased incidence of HPV-related HNC has been universally attributed to changes in sexual norms: earlier age of sexual debut (D'Souza et al., 2007b)(Schwartz et al., 1998)(Kreimer et al., 2004)(Heck et al., 2010), higher number of lifetime vaginal sex partners (D'Souza et al., 2007b)(Schwartz et al., 1998)(Maden et al., 1992)(D'Souza et al., 2009)(Rajkumar et al., 2003)(Rosenquist et al., 2005) and higher number of lifetime oral sex partners (D'Souza et al., 2007b)(Schwartz et al., 1998)(Kreimer et al., 2004)(D'Souza et al., 2009)(Rajkumar et al., 2003)(Rosenquist et al., 2005). However, given the colinearity of sexual behaviours, it is difficult to differentiate which behaviours are associated with oral HPV transmission from the literature.[4] The strong association of sexual behaviour with increased odds of HPV-related HNC is not observed for HPV-unrelated HNC, which are primarily caused by alcohol and tobacco use (Gillison et al., 2008). The increase in HPV-related HNC in the US is seen in a cohort born after 1950 and the cancer is seen as a legacy of the sexual liberation of the 1960s and 1970s (Chaturvedi et al., 2008).

[4] As sexual behaviours are colinear - people who have a higher number of partners for 1 sexual act tend to have a higher number of partners for other sexual acts as well.

Although it is clear that HPV is an important cause of HNC, infection with HPV is neither a necessary nor sufficient cause of HNC (cancer can occur in the absence of HPV and not all oral HPV infections lead to malignant transformations)(Gillison and Lowy, 2004). The obvious pertinent risk factor is persistent oral HPV infection for the development of HPV-related HNC: there have, however, been few studies investigating the natural history of oral HPV infection.

Oral HPV Prevalence

The seminal population-level study (Gillison et al. 2012) in the US, estimated that the prevalence of any HPV type in the oral cavity for both men and women (aged 14-69 years) is approximately 6.9% (95% CI, 5.7%-8.3%).[5] However, when separated by gender (Figure 3), it is significantly higher in men than women (10.1% [95% CI, 8.3%-12.3%] vs. 3.6% [95% CI, 2.6%-5.0%], P < .001; unadjusted prevalence ratio [PR], 2.80 [95% CI, 2.02-3.88]).[6] Oral HPV infection followed a bimodal pattern with respect to age, with peak prevalence among individuals aged 30 to 34 years (7.3%; 95% CI, 4.6%-11.4%) and 60 to 64 years (11.4%; 95% CI, 8.5%-15.1%). It is perhaps interesting to note that the prevalence of oral 'high risk' HPV-16 was only 1.0% (95% CI, 0.7-1.3%).

[5] A cross-sectional study was conducted as part of the National Health and Nutrition Examination Survey (NHANES) 2009-2010, a statistically representative sample of the civilian noninstitutionalized US population.

[6] In this study, associations with age, sex, number of sexual partners, and current number of cigarettes smoked per day were independently associated with oral HPV infection in multivariable models (Gillison, 2012).

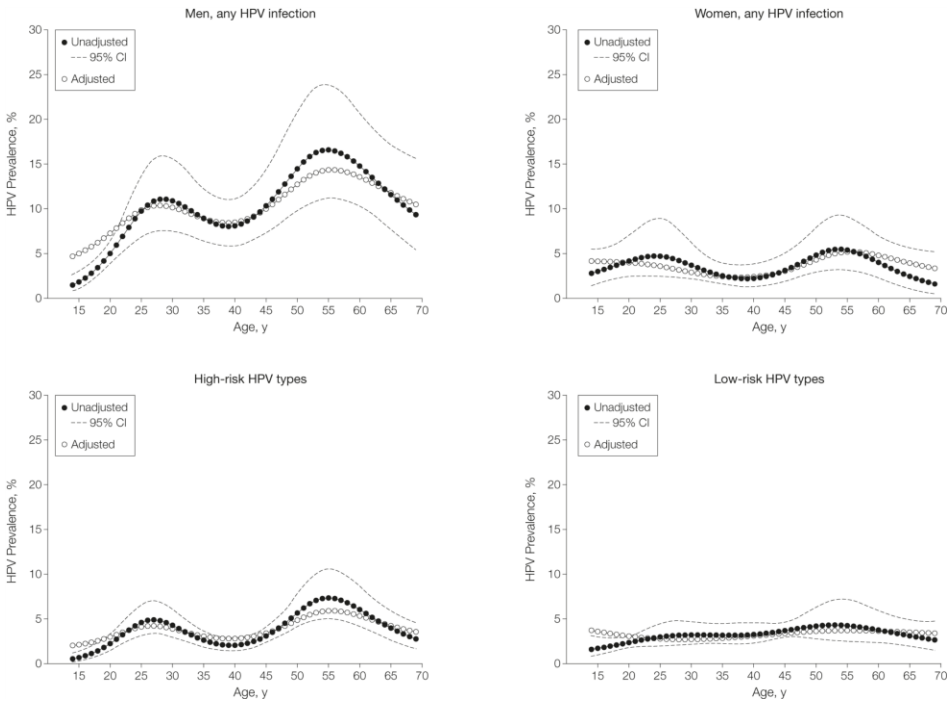

Figure 3: Oral HPV infection in the United States 2009-2010 (Gillison et al. 2012)

2.4 Epidemiology of Head and Neck Cancer in the HPV era

HNC is the fifth most common cancer diagnosed worldwide (Parkin et al., 2005) and the eighth most common cause of cancer death (Santarelli et al., 2009). Cancer registries around the world collect data on the number of cancers in specific anatomical locations. The World Health Organization (WHO)'s International Classification of Diseases (ICD) methodology is often used for this purpose. Unfortunately, the ICD format does not collect data on the cause of cancer and therefore the estimate of the number of HPV-related HNC can only be based on a proxy method of associated sites and then attributing the proportion that are HPV-positive based on local pathology results.

Worldwide

On a global front, the GLOBOCAN database is available to analyse data geographically. The incidence of oral cavity, larynx and pharynx cancer varies widely by region (Figure 4). Most of the known geographic variability in HNC incidence may be explained by the differential exposure to the major risk factors of HNC.

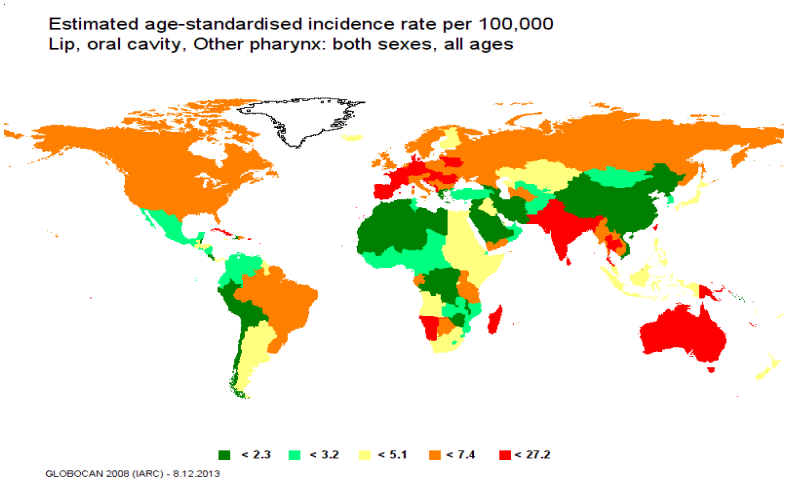

Figure 4: GLOBOCAN World map depicting age-standardized incidence rates (per 100,000 people) of cancers arising from the lip, oral cavity and pharynx

Europe

In Europe, incidence trends of HPV-related HNC increased significantly between 1998 and 2002 {Annual Percentage Change (APC) = +3.37, P<0.05}. HPV-unrelated HNC incidence in Europe also increased from 1988 until 1998 (APC = +1.73; 95% CI 1.2, 2.3), but seemed to plateau after 1998 (APC = -0.8; 95% CI -3.0, 1.5)(Licitra et al., 2006). Researchers from the pharmaceutical company, Sanofi Pasteur MSD, have looked at HPV-related cancers in European men (Hartwig et al., 2012) and have shown that cancers of the head and neck start occurring between 30 and 35 years of age and peak in the sixth decade of life (Figure 5).

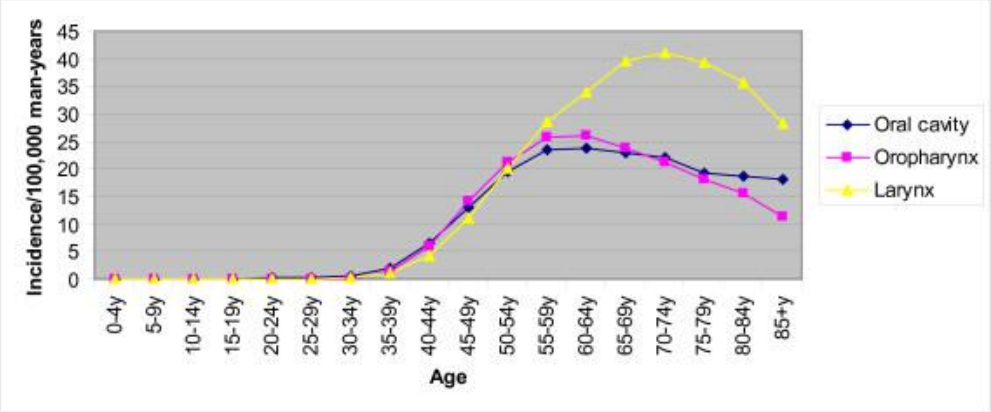

Figure 5: Incidence of HNCs, irrespective of HPV status in men in Europe by age group (Hartwig et al., 2012)

For 2008, a total of 67,354 (bounds: 63,443 - 71,292) new cases of HNC were estimated to occur in men in Europe. The authors assumed an HPV prevalence between 16.0% and 28.2% for cancer of HPV-related subsites, the expected number of new HPV-related HNC cases in European men was estimated to be 14,098 (bounds: 11,455-17,077) of which 12,707 are attributable to type-16 and 18 (Hartwig et al., 2012). This assumption regarding HPV prevalence is much lower than the latest estimates from the US (72%), discussed in chapter 3.1, which has implications for

estimating the economic burden of HPV-related HNC, discussed in chapter 3.2.

High-Income Countries

In England, the age-standardised incidence rates (ASIR) for potentially HPV-related HNCs increased by 160% for males from 1990 to 2008 and by 110% for females. Although the trends were less marked, increases in comparison to non-HPV related HNC for males and females (of 14% and 50% respectively) were also observed (NCIN, 2012). A Canadian study also showed that HPV-positive HNC substantially increased (25% vs. 62%, $p < 0.002$) over a period from 1993 to 2011 (Nichols et al., 2013). In Australia, between 1982-2005, there were significant annual increases in tonsil {1.39% (95% CI: 0.88, 1.92%)} and base of tongue cancers in males {3.02% (95% CI: 2.27, 3.78%)} and base of tongue cancer in females {3.45% (95% CI: 2.21, 4.70%)} (Hocking et al., 2011).

In South Korea, cancer registry data have observed increases in oropharyngeal cancer incidence over the last three decades - HPV-related sites (oropharynx) had increased significantly over the period 1999 to 2009 (APC = 2.35%, P = 0.017), particularly in young men (30-59 years, APC = 2.65%, P = 0.031), whereas HPV-unrelated sites such as larynx and hypopharynx decreased markedly in both sexes (Shin et al., 2013). Another study from Stockholm, Sweden, using a hospital based registry also observed a significant increase in HPV-related HNC over the last 20 years - the percentage of oropharyngeal cancers in patients with HPV-16 in Stockholm has risen from 23% in the 1970s to 57% in the 1990s and to 93% in the last recorded period from 2006 to 2007 (Näsman et al., 2009).

Though there is variability around the world in the extent of the increase in HPV-related HNC, there is little doubt that in epidemiological terms an epidemic (more disease than is anticipated) is occurring predominately in

the developed world among men (See chapter 3 for discussion of US data). When it comes to forecasting the likely economic burden of this disease, various epidemiological metrics are important to inform policy-makers. Moreover, decision-makers within the healthcare system are faced with challenges in ensuring that treatment services are delivered appropriately and efficiently. This has implications for workforce training, imaging and pathology requirements and drug budgets at local and national level.

Survival Rates of HPV-related HNC

Significant improvements in 5-year survival rate for oropharyngeal cancer have been reported in a number of geographic regions (van Monsjou et al., 2010). A number of meta-analysis and systematic reviews have examined survival in relation to HPV-related HNCs (O'Rorke et al., 2012)(Dayyani et al., 2010)(Ragin and Taioli, 2007). O'Rorke et al.'s (2012) systematic review and meta-analysis (N=42 studies) comprehensively examined disease-specific mortality, progression and recurrence of disease in HPV-related HNCs. Their principal finding is that patients with HPV-positive HNC had a 54% better overall survival compared to HPV-negative patients {Hazard Ratio (HR) 0.46 (95% CI 0.37 – 0.57)}. In terms of five-year relative survival rates, studies have reported between 70-80% vs. 25-40% comparing HPV-positive to HPV-negative HNC respectively, with these differences independent of age, gender and tumour stage. The economics of survivorship shall be elaborated further in chapter 5.

2.5 Treatment & Management of HPV-related Head and Neck Cancer

The survival and positive outcome of HPV-related HNC is better than non HPV-related HNC; an outcome thought to hold true for both surgical and nonsurgical modalities (Licitra et al., 2006)(Fakhry et al., 2008)(Gillison, 2010)(Gillison, 2009). With a greater likelihood of survival and a longer life span over which long-term complications (especially swallowing difficulties) of treatment may manifest themselves, the choice of optimal treatment modality becomes even more imperative for these patients and for those financially responsible for the cost of their care (Li and Richmon, 2012). Current treatment guidelines {such as the National Comprehensive Cancer Network (NCCN) in the US} do not use HPV status to dictate treatment (Li and Richmon, 2012), but this is likely to change once the results of major US multi-centred clinical trials are published.

Treatment Associated with Swallowing Complications

It is now clear that the high-dose chemotherapy and altered radiotherapy fractionation strategies, which contributed to improvements in survival rates, are also associated with an increased risk of developing late swallowing complications (Machtay et al., 2008)(Langendijk et al., 2009)(Frowen et al., 2010).[7] Surgery of oropharyngeal cancers has evolved from extensive open approaches with significant morbidity to minimally invasive approaches through the mouth (Li and Richmon, 2012). Transoral laser microsurgery and transoral robotic surgery (TORS) are two different techniques of transoral endoscopic surgery (TES) that can achieve complete oncologic tumour resection without cosmetic deformity while optimizing functional rehabilitation. Advocates of surgery argue that

[7] Fractionated Radiotherapy – The spreading out of the administration of radiation over time. Fractionation regimens are individualized between different radiation therapy centers. In North America, Australia, and Europe, the typical fractionation schedule for adults is 1.8 to 2 Grays per day, five days a week.

the assertion of lower morbidity is associated with nonsurgical, so-called 'organ-preservation' treatment is now being challenged by these new, expensive techniques of TES and TORS (Li and Richmon, 2012).

Traditionally, HNC patients have lower Quality of Life (QoL) and functional outcomes compared to their peers (Hammerlid and Taft, 2001). This reduction in QoL may be caused by the effects of advanced disease and the subsequent treatment affecting speech and swallow function, as well as the psychological effects of loss of function and physical disfigurement (Colangelo et al., 1996)(Rogers et al., 2002)(Seikaly et al., 2003). At JHMI, intensive pre- and post-treatment speech-language therapy is standard to improve patients chance of having better functioning post-treatment (Tippett and Webster, 2012). Also, patients with HPV-related HNC are at increased risk relative to traditional HNC patients for emotional distress because of their younger demographic and the stigma of acquiring a virus that is transmitted sexually (Gold, 2012). Therefore, stratifying by HPV status, it is likely that patients with HPV-related HNC from a higher socioeconomic background will have a different healthcare utilisation mix and length of engagement with healthcare system than those that are HPV-unrelated. The main differences in HNC stratified by HPV status are set out in Table 1.

Table 1: Differences between HPV-positive and HPV-negative Head and Neck Cancer

	HPV-positive tumours	HPV-negative tumours
Anatomical site	Tonsil and base of tongue	All sites
Age	Younger cohorts	Older cohorts
Sex ratio	3:1 men	3:1 men
Risk factors	Sexual behaviour	Alcohol and Tobacco
Social status	Higher	Lower
Incidence	Increasing	Decreasing
Survival	Improved	Unchanging

As HPV's role in HNC becomes clearer, the demand for diagnosis, treatment and management services in the developed world will change. Greater specificity as well as different patient socio-demographic profiles will prompt changes to and therefore investment along the cancer care pathway from cancer prevention strategies through to palliative care.

2.6 HPV-related Head and Neck Cancer & Public Health

The appropriate public health response does not wait for a disease to occur in the population. The strategy would always be to try and anticipate the likely burden and invest in preventing the disease from occurring in the future. But, when the disease happens, then the onus is to provide the best evidence to organise and finance the health system to enable those with disease-induced health needs to have access to high quality care. Often the starting point for policy-makers in the discussion on resource allocation for prevention strategies is a monetary estimate of the burden of the disease.

Economic Burden

A review by Merck Sharpe Dolme of the economic burden of non-cervical cancers attributable to HPV in Europe produced a total of 21 references from seven countries (Denmark, France, Germany, Greece, The Netherlands, Portugal, and the UK) (Préaud and Largeron, 2013). About half (11/21) of these studies had HNC estimates attributable to HPV. For example, in France, the overall costs of HPV-related cancers (Figure 6) in men was €107.2 million (in 2008), driven mainly by HNC (€94.6 million) and the total costs in women were €132.5 million, due mainly to invasive cervical cancer (€83.9 million)(Borget et al., 2011).

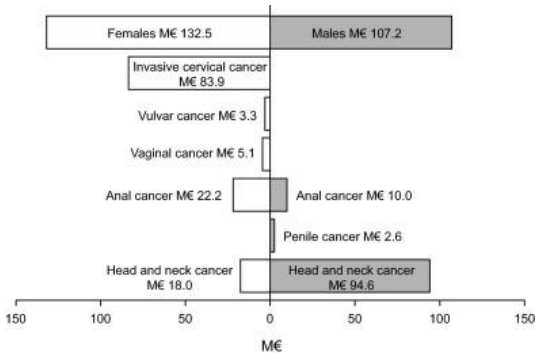

Figure 6: Estimated costs of HPV-associated cancers in France (Borget et al., 2011)

Apart from cervical cancer, an Italian study showed that HNC was responsible for the highest annual burden of direct costs among the HPV 6, 11, 16, and 18-induced malignancies (€59.1 million in €2011), followed by anal cancers (€6.7 million), vulvar cancers (€6.2 million), vaginal cancers (€2.7 million), and penile cancers (€2.0 million)(Baio et al., 2012) (Figure 7).

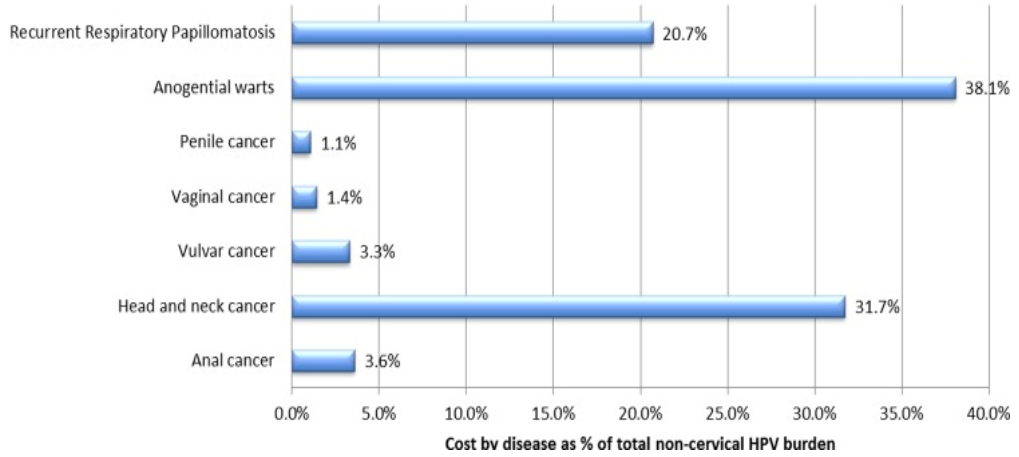

Figure 7: Burden of noncervical HPV 6,11, 16 and 18-related diseases (Baoi et al. 2012)

Attempting to derive estimates of the economic burden of HPV-related HNC in the US shall be explored in chapters two and three of this thesis. Often economic burden estimates are used to draw policymakers' (and the public's) attention to the likely scale of the problem in an attempt to prevent it from occurring (Frick et al., 2007).

Knowledge and awareness of the disease and possible preventive strategies is a theme of this thesis, the following section outlines the current state of the science with respect to prevention strategies.

Primary Prevention

Evidence of the effectiveness of the HPV vaccination in girls, by virtue of the near disappearance (<5%) of genital warts in Australia has been described as a huge boost for the public health community (Read et al.,

2011)(Ali et al., 2013)(Barton and O'Mahony, 2013)(Tabrizi et al., 2012). As of February 2013, HPV vaccination has been extended to include boys in schools in Australia. It has been predicted that genital warts will be almost eliminated in Australia in the near future (Korostil et al., 2013). There are also some promising indications for the role of HPV vaccination against cancer. However, uncertainty will remain until evidence of reduced abnormal pap smears is published in about 10-15 years. In the meantime, observational evidence suggests that the role of vaccination among women who had surgical treatment for HPV-related disease (i.e. cervical cancer) significantly reduces the incidence of subsequent HPV-related diseases including cancer (Joura et al., 2012).

Until 2012, none of the prophylactic vaccine studies performed had evaluated oral HPV infection or oral immunity to HPV and therefore the vaccine's impact on the incidence of HPV-related HNC remains an open question (Best et al., 2012). In 2013, a study from Costa Rica showed that HPV prevalence four years after vaccination with the 'bivalent' HPV16/18 vaccine (Cervarix®) was much lower among women in the vaccine arm compared to the control arm, suggesting that the vaccine affords strong protection against oral HPV16/18 infection (Herrero et al., 2013).

Following on from Australia, provinces in Canada such as Prince Edward Island and Alberta are also starting to roll out a school-wide vaccination programme to include boys in the HPV vaccination schedule.[8] Evidence of the efficacy of the quadrivalent HPV vaccine in preventing infection with HPV-6, 11, 16, and 18 and the development of related external genital lesions in males 16 to 26 years of age has been demonstrated in over 4,000 participants from eighteen countries (Giuliano et al., 2011b). The

[8] HPV vaccine program expanded to boys in Alberta.
Source: http://www.cbc.ca/news/canada/edmonton/hpv-vaccine-program-expanded-to-boys-in-alberta-1.2452361 (Last accessed 15/12/13).

hope is that the vaccine will also be effective against oral HPV infections and subsequent cancers.

The cost-effectiveness of vaccinating boys has been broached by a number of researchers (Kim and Goldie, 2008)(Kim and Goldie, 2009)(Chesson et al., 2011)(Elbasha and Dasbach, 2010). The common consensus has been that achieving high-rates of vaccinating girls will offer 'herd protection' to boys and would be more cost-effective strategy (Kim and Goldie, 2009). This strategy neglects the fact that sexual networks are not restricted by geographical borders or protect the men who have sex with men (MSM) population from the virus. One of the biggest methodological issues with these estimates is the poor quality of data regarding the cost-per-case of oropharyngeal cancer and the underestimation of the percentage of cases caused by HPV-16/18. This is issue is revisited in the next chapter.

Secondary Prevention

The aim of screening is to identify asymptomatic disease, by testing a population that has not yet developed clinical symptoms. Traditionally, oral cancer screening consists of visualisation and palpitation by a trained medical professional. Evaluation of screening for oral cancer in high-risk males has been conducted and reported to be cost-effective in the United States (Dedhia et al., 2011). However, in 2013, the United States Preventive Services Task Force (USPSTF) deemed the evidence to support routine oral cancer screening in any cohort was insufficient (Olson et al., 2013)(Mitka, 2013). In the UK, a full Health Technology Assessment (HTA) has been conducted on a number of strategies including invitational and opportunistic screening by general dental and medical practices (Speight et al., 2006). The conclusion of this HTA was that opportunistic high-risk screening, particularly in general dental practice, might be cost-effective

(Speight et al., 2006). [9] An easily recognisable sign of HPV-related HNC is a pea-sized, immovable lump under the chin. This may be something that General Practitioners (GPs) are currently unaware of. As HPV-related HNC has become more commonly diagnosed in secondary care, the importance should be on communication methods to educate GPs on recognising the signs and symptoms of HPV-related HNC.

Recent developments in oral cancer screening includes using fluorescent lights (Rahman et al., 2010)(McNamara et al., 2012) and staining (Riaz et al., 2013)(Macek, 2011) to detect cell structure changes in the oral cavity. However, none of these methods detect the early signs of HPV-related HNC. Given the inaccessibility of the oropharynx and lack of known precancerous lesions, a screening technique similar to cervical cancer is unlikely to ever happen. Early detection may be possible by using a simple blood test. Using the European Prospective Investigation into Cancer and Nutrition cohort, IARC investigators showed that HPV-16 E6 seropositivity was present more than ten years before diagnosis of HPV-related HNC (Kreimer et al., 2013).

The 2013 EUROGIN congress for HPV researchers, identified topics such as the cost-effectiveness of the new nanovalent HPV vaccine and the need for 3 doses of HPV vaccination for full immunity as the most pressing public health questions. [10] Again, to inform these models appropriate cost-per-case estimates of HPV-related HNC are needed.

[9] The cost-effectiveness threshold in the UK is £20,000 to £30,000 per Quality Adjusted Life Year (QALY)

[10] http://www.eurogin.com/2013/ -The congress is one of the largest forums worldwide for clinicians interested in cervical cancer control and HPV-associated disease (accessed: 4th April 2014)

2.7 HPV-related Head and Neck Cancer in Ireland

As other jurisdictions (especially the UK) consider gender-neutral HPV vaccination, Irish policy-makers will come under public pressure to also make a decision to invest substantial finances (estimated to be ~€8-12 million per annum) to vaccinate boys as part of the childhood immunisation program. Decision-makers will request that the national's HTA agency - the Health Information and Quality Assurance (HIQA) - conduct the economic evaluation. The problem HIQA is likely to face is in obtaining the relevant epidemiological and cost data to populate their model.

Clinical Literature

The earliest clinical report of HPV and disease in the oral cavity in Ireland was an association between HPV and oral lichen planus from 2003 (O'Flatharta et al., 2003).[11] In 2008 and 2009 the causal role of HPV in HNC was not subsequently empirically demonstrated by Irish lab-based researchers (O'Regan et al., 2008)(Toner and O'Regan, 2009). By 2010, the Irish otolaryngology community recognized that this epidemic existed in Ireland but that empirical data was lacking here (Heffernan et al., 2010)(O'Connor et al., 2010). These reports highlighted the fact that testing for HPV in suspected patients has only very recently become part of routine care in Ireland.

Epidemiology

The primary activity of the National Cancer Registry of Ireland (NCRI) is to maintain a national database of all new cancers. The NCRI annual statistics shows that the number of oropharygneal (i.e. base of tongue, tonsil and

[11] Oral lichen planus (OLP) is a chronic relapsing cell-mediated condition of unknown aetiology.

oropharynx) cancers from 1994 to 2010 in Ireland has doubled (Figure 8). These cancers that are related to HPV, and though it is not clear exactly how many can be attributed to HPV infection, it is likely that the proportion has increased.

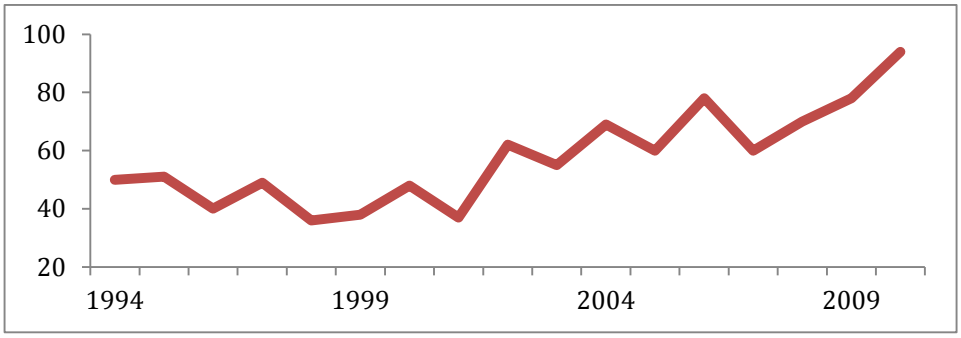

Figure 8: Number of oropharyngeal cancers in Ireland per annum from 1994 to 2010 (NCRI, 2013)

Future Direction

The momentum in clinical research will continue in the Republic of Ireland as routine HPV testing of HNC becomes commonplace. However, what is urgently required is a national biobank to store cancerous tissue for future analysis similar to what is available in Northern Ireland. This would allow for retrospective testing for causal agents like HPV. From an economic perspective, what is lacking in Ireland (and elsewhere) is the collection of pertinent data (e.g. cost-of-care of a case of HPV-related HNC) to help facilitate decisions regarding allocation of scarce resources for treatment and survivorship care. Such data would also help inform models to estimate the cost-effectiveness of gender-neutral HPV vaccination.

Given the rise in HPV-related cancers across the developed world, the clamour from the scientific community in Ireland for gender-neutral HPV vaccination will increase.[12] The efficacy of the vaccine against genital

[12] "Call for HPV vaccine to cover boys" Source: http://www.rte.ie/news/2014/0502/614769-hpv-vaccine/ (accessed: 2nd May 2014)

warts in Australia has made those in the HPV community hopeful of the effectiveness of the vaccine in HPV-related cancers in men. Ideally, the debate on this issue in the public domain would be evidence-based and informative. Before then, chapters 3 and 4 elaborates on characterising the burden of this cancer and chapter 5 empirically looks at healthcare utilisation of cancer survivors that would include HPV-related HNC but unlikely to include HPV-unrelated HNC. Chapter 6 discusses some of the challenges and economic perspective on HPV and cancer communication.

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Chapter 3: HPV-related Head and Neck Cancer in the United States – The Epidemiological and Economic Burden

Cancer is a major public health issue (Brown et al., 2001) and more than 14 million people are diagnosed with cancer each year around the World.[13] The signing of the *National Cancer Act* of 1971 provided an extra $100 million to find a cure for cancer by then President Richard Nixon.[14] The passing of this *Act* through congress is generally viewed as the beginning of the *'War on Cancer'.* Subsequent American governments have developed plans including the current Obama administration to tackle the burden of cancer. How burden is described, measured and whose perspective is used is critical in characterising the 'burden' of any disease.[15]

Burden of Illness

The word 'burden' can take on many different meanings in cancer care depending on perspective. The patient, who endures the physical and mental stress of having cancer, carries the most significant burden as they live their daily lives with the disease. Then, there is the informal or caregiver burden that family or friends of someone with a cancer diagnosis copes with. This gives rise to aspects of the societal burden. The

[13] Global cancer cases reach 14 million. Source: http://www.bbc.co.uk/news/health-25346639 (Last accessed: 14th April 2014)

[14] Milestone (1971): President Nixon declares war on cancer. http://dtp.nci.nih.gov/timeline/noflash/milestones/M4_Nixon.htm (Last accessed: 29/12/13).

[15] Prior to his death (March 26th 2009), Senator Edward Kennedy brought the *21st Century Cancer Access to Life-Saving Early Detection, Research and Treatment (ALERT) Bill* to congress. The *Bill* set out to modernise the *National Cancer Act* of 1971 and increase access to preventive healthcare in the fight against cancer. The intent of the Bill was also to invest in deadly cancers (defined as those cancers with <50% survival at 5-years) and rare cancers (defined as <15 cases per 100,000 or <40,000 new cases per year (NCI Cancer Bulletin, 2010). Source: http://legislative.cancer.gov/topics (Last accessed: 29th December 2013).

employer burden in the form of productivity losses, sick leaves pay and friction costs in finding a replacement during an employee's treatment and recuperation. Finally, there is the burden on the healthcare system and the public purse. In the US the healthcare system includes both private health insurance companies and governmental agencies.

The main comparative burden measures across disease states are epidemiological {e.g. incidence and mortality, potential years of life lost (PYLL), and prevalence}, economic (e.g. direct medical expenditure, productivity losses, losses to tax revenue) and quality of life (e.g. activities of daily living) in nature. Established in the 1960s, the methodology most associated with measuring the economic burden of any disease is known as a cost-of-illness (COI) study (Rice, 1966). COI studies are descriptive analyses assessing the economic burden of health problems on the population overall (Larg and Moss, 2011). The perspective and methodology used can greatly impact cost estimates and varies between studies (Table 2) (Segel, 2006).

Table 2: Costs included in cost-of-illness study by perspective (Segel, 2006)

Perspective	Medical Costs	Morbidity Costs	Mortality Costs	Transportation/ Nonmedical Costs	Transfer Payments
Societal	All costs	All costs	All costs	All costs	–
Health care system	All costs	–	–	–	–
Third-party payer	Covered costs	–	Covered costs	–	–
Businesses	Covered costs (self-insured)	Lost productivity (Presenteeism/ Absenteeism)	Lost productivity	–	–
Government	Covered (Medicare, Medicaid)	–	–	Criminal justice costs	Attributable to illness
Participants and families	Out-of-pocket costs	Lost wages/ Household production	Lost wages/ Household production	Out-of-pocket costs	Amount received

The traditional COI approach considers 'direct medical' costs, 'productivity' costs, and 'intangible' costs. Together with prevalence and

incidence, morbidity and mortality help portray the overall burden of disease on society (Rosen and Cutler, 2009). 'Direct medical' costs are associated with physician services, diagnostic procedures, laboratory tests, emergency department and hospital services, medications, treatments, ancillary therapies, and other healthcare services that can be directly attributed to the disease which includes treatment for pain and depression. 'Indirect' or 'Productivity' costs result from lost work productivity, disability and premature death due to a disease or condition. 'Intangible' costs are primarily related to losses in quality-of-life (e.g. pain and suffering).

Prevalence vs. Incidence Costing Methods

The prevalence cost of a disease are often reported for a specific calendar year, and are based on the costs of medical care in that year for all individuals diagnosed with or living with the disease (Barlow, 2009). Prevalence cost estimates thus encompasses care delivered to individuals across the disease trajectory, including the newly diagnosed, the long-term survivors, as well as those at the end-of-life (In chapter 4, the annual cost of HNC using MEPS is estimated). Prevalence cost estimates can be used to inform health policy decisions on the structure of insurance benefits, (spending-level-based) eligibility criteria for public programs, and budgeting for future program costs (Lipscomb et al., 2009). In contrast, cost estimates using incidence cases include only the newly diagnosed, and are typically longitudinal estimates of medical costs following diagnosis with disease (Barlow, 2009). When applied in cost-effectiveness analysis (CEA), incidence cost estimates can be useful inputs for policy decisions about coverage of interventions to prevent or treat disease or for specific treatments (Lipscomb et al., 2009).

All these 'burden' metrics can help inform the allocation of research and healthcare resources across cancer categories, and to evaluate the

potential costs and benefits of public health interventions (Romano et al., 1995).[16] Notably, as stated by Ramsey (2008) in an editorial based on a study on productivity losses due to cancer: *"Perhaps the primary benefit of monetary estimates is simply to translate what professionals and patients already know about the human costs of cancer into a metric that is universally understood. As a tool for advocacy, dollar values can be powerful, particularly when they are weighed against other programs that influence human life and health under limited budgets"*.

Objective

To characterise, discuss and elaborate upon the known burden of HNC in the US incorporating the focus on HPV. Epidemiological metrics will highlight the epidemic nature, significance (with respect to other HPV-related cancers) and the longer survivorship phase of the cancer. A literature review of the economic burden will highlight the nuances of this research. Finally, I will discuss the nature and components of a COI study with relation to HPV-related HNC in the US.

[16] There is a battery of standardised epidemiological, biomedical, behavioural, psychosocial and economic metrics to measure the many aspects of population health with respect to a heterogeneous disease like cancer and help establish public health goals. These metrics allow analysts to compare national health status and the performance of health systems across countries (Murray and Lopez, 1997).

3.1 Epidemiological Burden of HPV-Related Head and Neck Cancer in the US

Each year, the American Cancer Society (ACS) estimates the numbers of new cancer cases and deaths expected in the United States in the current year. Estimates are based on incidence data from the NCI, the Centres for Disease Control and Prevention (CDC), and the North American Association of Central Cancer Registries while mortality data comes from the National Center for Health Statistics (NCHS) (Siegel et al., 2012). Figure 9 shows that the estimated incident cases of cancers associated with HPV in the tongue, mouth, pharynx and other oral cavity by gender over the time period 2004 to 2012. The ratio of males to female is of the order of 3:1. The definition of epidemic given by epidemiologists is more disease than is anticipated by previous experience (Green et al., 2002) and HPV-related HNC has the hallmarks of an epidemic.

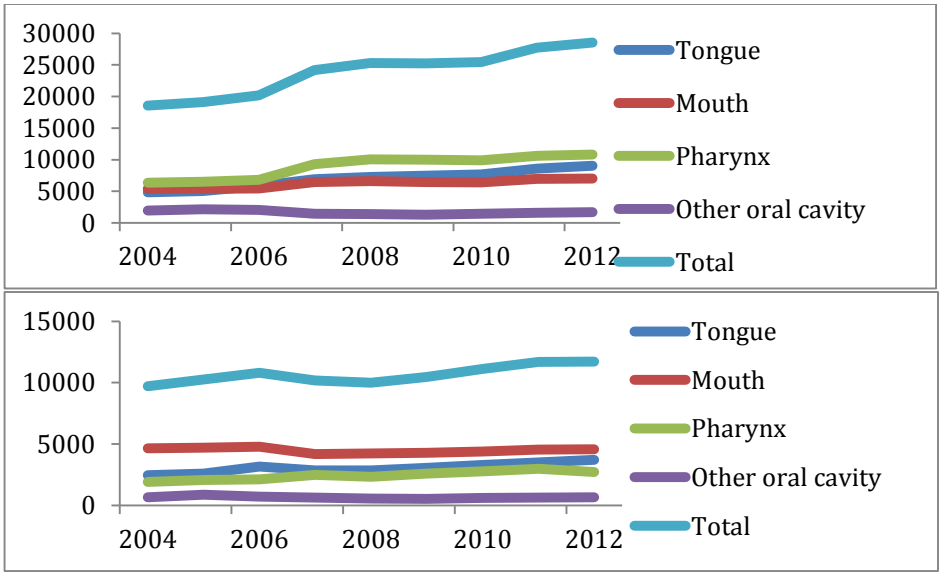

Figure 9: Estimated new oral cavity & pharynx cases, males (Top) and females (Bottom) in the United States (ACS, 2013)

The CDC report the numbers of new cancer cases attributable to HPV each year on their website (Figure 10).[17] The CDC (2014) uses population-based data from cancer tissue to estimate the percentage of these cancers that are probably caused (implicated) by HPV. The CDC estimate of the attributable fraction of cancer caused by HPV is based on the latest epidemiological evidence (CDC 2014). It is expected that HPV-related cancers in the oropharynx will surpass cervical cancer by 2020 in the US if current trends persist (Chaturvedi et al., 2011).

Cancer site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)			Percentage probably caused by HPV	Number probably caused by HPV		
	Male	Female	Both Sexes		Male	Female	Both Sexes
Anus	1,687	3,084	4,771	91%	1,500	2,800	4,300
Cervix	0	11,279	11,279	91%	0	10,300	10,300
Oropharynx	9,312	2,317	11,629	72%	6,700	1,700	8,400
Penis	1,003	0	1,003	63%	600	0	600
Vagina	0	694	694	75%	0	500	500
Vulva	0	3,039	3,039	69%	0	2,100	2,100
TOTAL	**12,002**	**20,413**	**32,415**		**8,800**	**17,400**	**26,200**

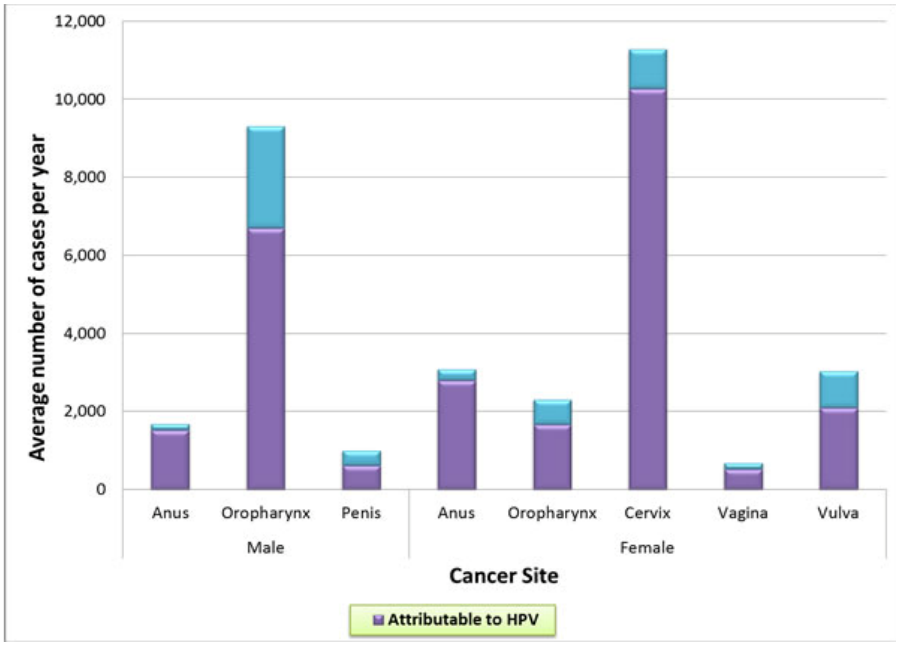

Figure 10: Estimated number of HPV-related cancers in the United States (CDC, 2014)

[17] An attempt to compare the medical expenditures of all HPV-related cancers using IMS Pharmetrics insurance data claims was attempted but was ultimately unsuccessful due to inability to access data.

HPV-related HNC Epidemic

Evidence of the HPV-related HNC epidemic in the US has been illustrated by other researchers (Marur et al., 2010)(Chaturvedi et al., 2011). In their analysis, Chaturvedi et al. (2011) used a more granular coding system - ICD for Oncology version 3 (ICD-O-3) codes. This allowed for lingual tonsil, palatine tonsil, base of tongue, oropharynx, and Waldeyer ring codes to be defined as HPV-related HNC.[18] In Figure 11, they found that between 1973 and 2004, the US incidence of HPV-related HNC increased significantly (APC = +0.80, P<0.001) especially among younger males. In contrast, the incidence of HPV-unrelated HNC decreased significantly during the same period (APC = -1.85, P<0.001).

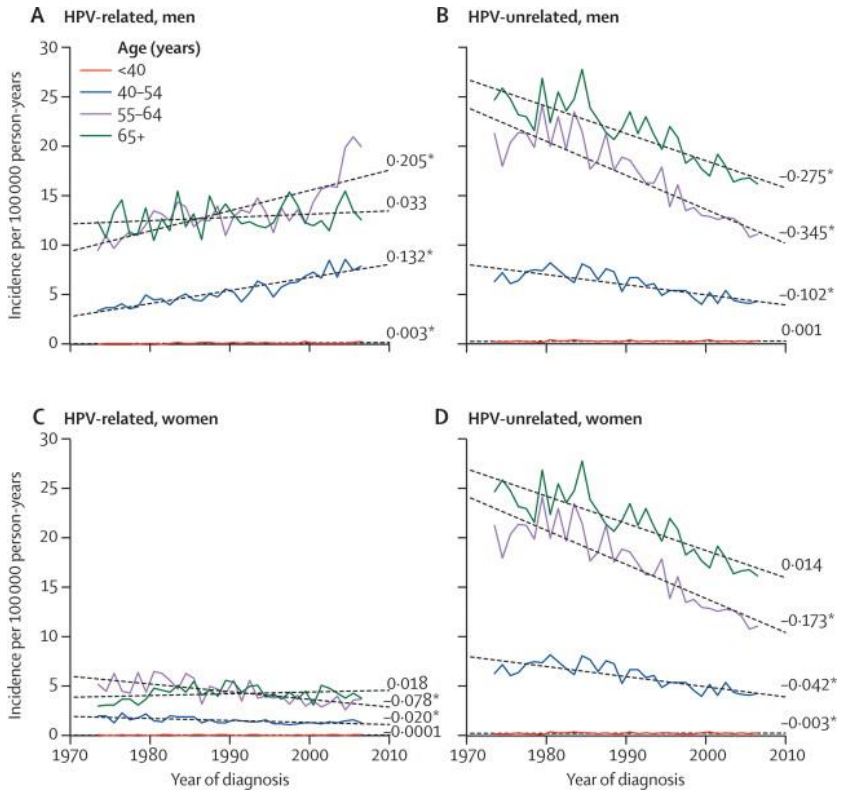

Figure 11: Age -adjusted incidence of HNC that were diagnosed between 1973 and 2006 in males and females at HPV-related (A: Males and C: Females) and HPV-unrelated sites (B: Males and D: Females) (Chaturvedi et al. 2011)

[18] Note they also used ICD-O-3 to define HPV-unrelated sites of the oral cavity, including tongue, gum, floor of mouth and palate (Chaturvedi et al., 2011).

Similar careful anatomic site stratification has also shown that the age-adjusted incidence of oropharyngeal cancer is rising dramatically – estimated by Sturgis and Ang (2011) to be running at annual increase of 5%.

Mortality Metrics

According to the ACS statistics, the estimated mortality rate for both genders of oral cavity & pharynx cancers in the US is estimated to be 8,000 deaths per annum (Figure 12).

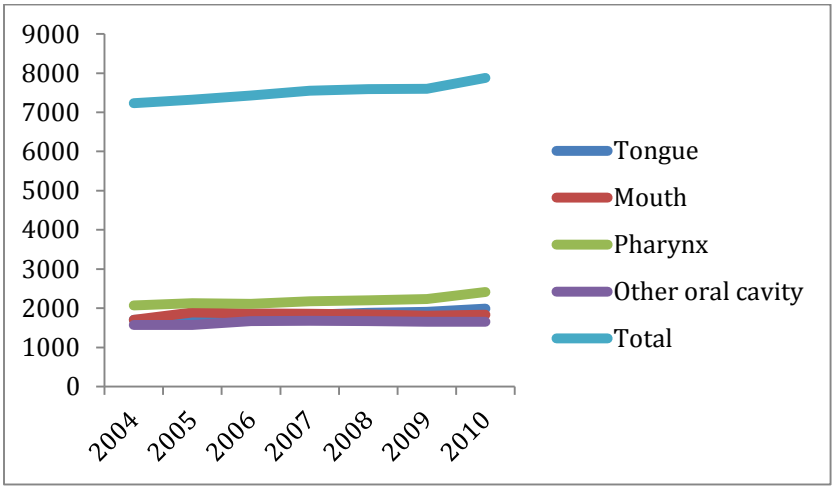

Figure 12: Estimated oral cavity & pharynx cancer deaths in the United States (ACS, 2013)

The slight increase in the number of people dying from oral cavity and pharynx cancer is likely to be related to those cancers caused by excessive tobacco and alcohol consumption. The prevalence (patients living with a history of HPV-related HNC) will increase based on the significantly favourable prognosis of these cancers (Sedaghat et al., 2009)(Gillison, 2009). The 3-year cancer-specific survival rate of HPV positive HNC is 93% for non-smokers, 70.8% for HPV-positive with a history of smoking and 46.2% for cancer not related to HPV (Ang et al., 2010).

An estimate of the likely economic burden (that follows) of a disease characterises the size of the problem to the extent and number of people

effected which can influence the pressure brought to bear on elected representatives to do something and through this mechanism inform the policy response. Economic burden studies give no indication of the cost of the addressing the problem (i.e. the efficiency issue) or how (scarce) resources should be invested in preventing, researching and treating the disease.

3.2 Economic Burden of HPV-Related Head and Neck Cancer in the US

This literature review of the economic burden of HPV-related HNC in the US builds upon previous economic reviews of HNC (Selke et al., 2001) (Lee et al., 2004) (Menzin et al., 2007). Those reviews were conducted prior to the full appreciation of the HPV link in HNC.

Objective

The objective was to identify studies that reported the economic burden of HPV-related HNC in the US.

Method

This review was carried out in November 2011. Only original study design (hypothetical models excluded) with defined populations and economic endpoints (e.g. Average cost per case) were considered. *Inclusion criteria*: The report addressed the costs of HNC in the US; patients were over 18; the study was published in English; and the study was published between 2000 and November 2011. *Exclusion criteria*: Reports that were non-US studies, no dollar amounts reported and that concentrated on HPV-unrelated HNC sites.

The search strategy was performed in PubMed. Searches of the following supplemental resources were then performed: Embase, Cochrane Library, Scopus, Web of Science, Medline Cancerlit, the Surveillance, Epidemiology, and End Results (SEER) program (from the NCI online database), American Society of Clinical Oncology (ASCO) proceedings (2000-2011). Economic databases searched included: Econlit, the Cost-Effectiveness Analysis (CEA) Registry, Centre for Reviews and Dissemination (CRD): NHS Economic Evaluation Database (EED), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) proceedings (2000-2011) and Society for Medical Decision Making (SMDM) proceedings

(2000-2011). Other sources included www.clinicaltrials.gov and International Standard Randomized Controlled Trial Number (ISRCTN) Registry. Comprehensive Internet searches using well-known search engines (i.e. Google Scholar) were also conducted to assist in the search for published articles.

The search used broad Medical Subject Headings [MeSH] and 'text only' search terms. *'Head and neck neoplasms'* [MeSH], AND *'Economics'* [MeSH] restricted to English language, age 19+ and publication date 2000-2012.[19] The initial search generated 246 references in Pubmed. Other searches included combining key-words such as '*cost'* and '*cost analysis'* with '*human papillomavirus', 'oropharyngeal cancer', 'oral cancer', 'mouth cancer' and 'head and neck cancer'.* Abstracts were reviewed from each reference and any references thought to be relevant were retrieved in full text (where possible). Specifically, studies were retrieved in full text if the abstracts contained any cost information regarding the economic burden associated with the screening, diagnosis, or treatment of HPV-related HNC. The electronic search was supplemented by a manual review of the bibliographies of review articles and original research articles that had been retrieved.

Results

In total, 7 articles were included of which 2 were abstracts from ISPOR conferences (See Figure 13).

[19] Online versions of articles to be print published in early 2012 were available at the time of the review.

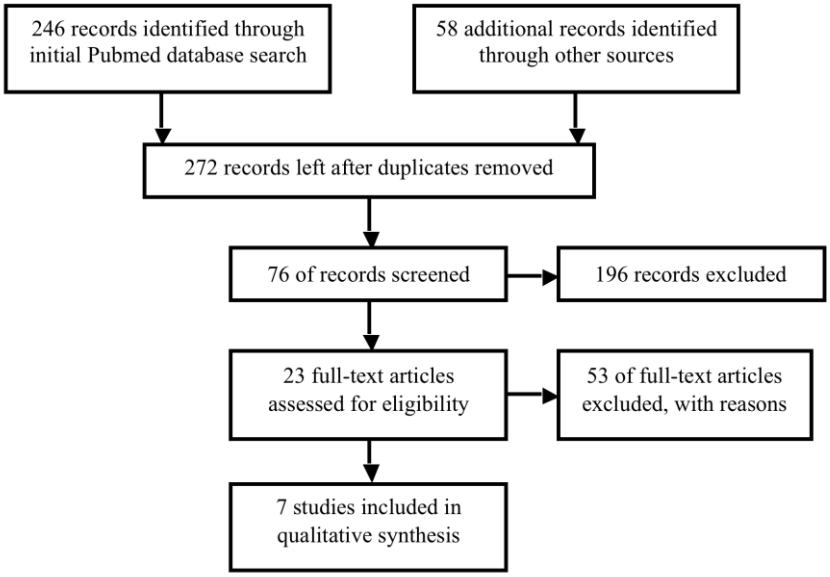

Figure 13: Literature review schema

Two of the seven studies (Table 3) estimated the economic burden of HPV-related HNC over a patient's lifetime. Hu and Goldie (2008) base their estimates on a previous study that looked at Medicare patients only (Lang et al., 2004). From the epidemiological evidence, we know that HPV-related HNC are predominately seen in patients aged 40-65yrs whereas Medicare claims are based on patients >65yrs.[20] This is a shortcoming in using this data source, also it should be noted that the evaluated patients were from 1991-1993, when combined modality therapy had not come into play (Amonkar et al., 2011). Subsequently, many economic evaluation use the average cost per case ($33,020) from this study in their cost-effectiveness model of gender neutral HPV vaccination (Kim and Goldie, 2008)(Kim and Goldie, 2009)(Elbasha and Dasbach, 2010)(Chesson et al.,

[20] http://www.aarp.org/health/medicare-insurance/info-04-2011/medicare-eligibility.html (accessed 18th March 2014)

2011). It is likely that this is a gross underestimation of the true 'cost' of a HNC (HPV related or not) given the use of multimodality treatment. [21]

An analysis by the CDC reported on the societal burden of mortality associated with HPV-related cancer sites for 2003 (Ekwueme et al., 2008). The authors used a human capital approach to estimate the mortality burden in terms of years of potential life lost (YPLL) and mortality-related productivity costs. Specific to oral cavity/pharynx, they estimated the present value of future lifetime lost productivity of HPV-related HNC cancer sites to be $1.37 billion, with men accounting for $1.1.billion (Ekwueme et al., 2008). The authors did not take into account the attributed fraction due to HPV, which would lower the burden estimates. However, this report does provide an upper bound estimate on what the productivity losses would be if all the cancers were HPV-related.

At a 2008 NCI 'State of the Science' meeting, the annual estimated cost for HPV-related oropharyngeal cancers of treatment and disease management was calculated to be in the order of $151 million (Chaturvedi in Adelstein et al., 2009). It is likely that this figure is a conservative estimate of the treatment cost burden as the cost of the treatment has risen substantially since then with multiple modality regimens coupled with increased incidence of HPV- related HNC.

[21]Although not a feature of this thesis, data obtained from 32 HNC patients from a local hospital in Baltimore {Greater Baltimore Medical Centre (GBMC)} showed that the average hospital charge is over $110,000 per patient. This figure does not include physician fees.

Table 3: Economic burden studies of HPV-related HNC in the United States

Author, Year & Type of patients	Cost Methodology	Data Sources	Cost Estimates	Main Conclusion & Limitation	HPV Focus
Hu & Goldie 2008 Report looked at non-cervical HPV-related conditions: Oropharyngeal and Mouth Cancer	Incidence-based approach applied to costs to estimate economic burden. Discounted Lifetime cost per case expressed in present value.	US – Linked SEER-Medicare data (Lang et al. 2004) British & Dutch studies used for plausible range American Cancer Society (2003) - incidence rates	Average cost per case of HNC in 2003 is $33,020 (Range: Min $15,340 – Max $46,800)	Total lifetime costs for new cases in 2003: $38.1m (Range: $17.7-54.1m) Uses SEER-Medicare claims data	Underestimated HPV prevalence. (10.7% of all oropharyngeal cancer caused by HPV-16, 18)
Ekwuene et al. 2008 HPV-associated cancers – Cancers of the tonsil, tongue and other oral cavity/pharyngeal cancers.	*Societal burden of mortality:* Mortality, Years of potential life lost (YPLL), value of productivity loss from premature death¶	SEER US census National Mortality data - CDC's NCHS National Vital Statistics system US life tables ICD-10	*Year (2003):* Number of deaths: 3,379 YPLL: 63,587 YPLL per death = 18.8 PVFLE: $406,061,000	Total mortality costs = $1.37bn (Discounted at an annual rate of 3%) Productivity loss per death = $406,061 Human Capital approach* used for productivity loss.	Used subsites as proxy for HPV-associated cancers.

Abbreviations and Footnotes: CDC – Centres for Disease Control and Prevention; HPV- Human papilloma virus; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Edition; NCHS – National Center for Health Statistics; PVFLE -present value of future lifetime earnings; SEER- Surveillance, Epidemiology and End Results; YPLL - Years of potential life lost.

¶Productivity costs of premature mortality were estimated by multiplying the number of deaths in 2003 (stratified by age, sex and race/ethnicity) by the PVFLE stratified by age and sex. The PVFLE estimates that were applied took into account factors like life expectancy, the labour force participation rate and future growth rate in productivity, and the imputed value of housekeeping services (e.g., cooking, cleaning, childcare)

*The human capital approach equates the value of a human life to the discounted market value of the output produced by an individual over an expected lifetime. This approach, which is the most commonly used, estimates the discounted value of future earnings that result from an extension or improvement in life

Five pertinent direct medical cost studies that looked at clinically diverse populations of HNC patients are given in Table 4. The range of patients evaluated, the cost methodology adopted, the length of data collection, and the data sources used differ among the studies. All these studies used the ICD-9/10 codes as the basis of their disease diagnosis. However, none of these studies considered the HPV association with HNC.

Two studies (Lang et al. 2005 and Epstein et al. 2007) used exclusively publicly funded cost sources – Medicare and Medicaid populations (Lang et al., 2004)(Epstein et al., 2008). These studies used public payment rates that may underestimate the economic burden of the disease as they capture only a subset of the general population. This is because as noted in a study (Choi et al. 2009) using a large US commercial managed care claims database (n=6,570), the average first year expenditures associated with HNC diagnosis in this population ($29,608) is higher than the projected average Medicare payment ($18,000) (Choi et al., 2009.).[22] This is because public payers reimbursement rates are typical lower. The other two studies also used private sector health cost data (Amonkar et al. 2011 and Le et al. 2011). They highlight the direct medical costs associated with specific types of HNC patients – those that had surgery or have metastatic or recurrent locally advanced cancer.

[22] Medicare achieve substantial economies of scale in terms of the prices it pays for health care and administrative expenses and, as a result, private insurers' costs have grown almost 60% more than Medicare's since 1970.
Source: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads//tables.pdf (accessed: 5th April 2014).

Table 4: US cost studies of HNC patients and the HPV perspective

Author, Year & Type of patients	Cost Methodology	Data Sources	Cost Estimates	Main Conclusion & Limitation	HPV Focus
Amonker et al. 2011 Resected squamous cell carcinoma of the head and neck (SCCHN) (N=1,104)	Retrospective claims-based analysis of commercially insured patients (2004-2007)	Medical, Pharmacy & laboratory data and enrolment information from a large US database of commercially insured patients.	Patients incurred ~$94 million in cost following index surgery. (Average: $85,000 per-patient - 2008 USD). Mean total healthcare cost was $34,450 per-patient per-year (2008 USD).	Patients with resected SCCHN incur substantial healthcare costs and have high utilisation rates. Managed care setting – not generalizable	Not mentioned in report. ICD-9 codes used to identify patients. Possible to separate by HPV-associated subsites.
Le et al. 2011 Metastatic (N=1,042) & recurrent, locally advanced (N=324) HNC	Retrospective payer-based analysis (2004-2008) Rate frequency and costs of healthcare utilisation during the 6-month post-index period were compared.	Thomson MarketScan databases (Medicare data & private sector health data from ~100 payers)	Any-cause total healthcare costs: - Unadjusted Metastatic HNC patients (n=1,042) = $65,412 ±74,181 (2008 USD) - Unadjusted Recurrent Locally Advanced HNC patients (n=324) = $25,837 ±43,460 (2008 USD)	*"Advanced HNC patients, pose a significant health economic burden on the payer"*. Based on patients receiving employer-sponsored health insurance - not generalizable	Not mentioned in poster. ICD-9 codes used to identify patients. Possible to separate by HPV-associated subsites.
Choi et al. 2009 Head and neck cancer diagnosis (N=6,570).	First year expenditures associated with head and neck cancer diagnosis in the US managed care population.	U.S commercial managed care claims database	Projected Average Medicare payment per individual in 1-year post HNC diagnosis = $18,000 (2007 USD) Average heath care cost per patient 1-	Annual cost associated with HNC is higher in managed care population than reported on Medicare population.	Not mentioned in abstract. ICD-9 codes used to identify patients. Possible to separate by HPV-associated subsites.

			year post HNC diagnosis = $29,608 (±77,500) (2007 USD)		
Epstein et al. 2008 Oral and pharyngeal squamous cell carcinoma (N=3,422)	Direct medical costs of patients were defined as being treated for early- or late- stage disease based on treatment modality.	Retrospective analysis of California Medicaid Claims Data. CPT-4 coding in claims data	Median Year-1 cost of care following initial diagnosis = $25,319 (n=229) (2002 USD) Estimated range of Year-1 cost of care in a commercial PPO in California = $42,198 - $72,340 (2002 USD)	Costs for patients treated as having early-stage OSCC were approx. 36% less than for those treated with late stage disease (p=0.002). Did not include patients that died within 1-year of diagnosis	Not mentioned in report. ICD-9 codes used to identify patients. Possible to separate by HPV-associated subsites.
Lang et al. 2004 Retrospective cohort analysis of newly diagnosed elderly (>65yrs) squamous cell carcinoma of the head and neck (N=4,536)	Linked clinical data to Medicare claims	SEER and Medicare claims Selected diagnosis related groups, ICD-9-CM diagnosis and procedure codes, and Healthcare Common Procedure Coding System codes in the Medicare claims data	Total mean Medicare payments = $48,847 IQ range: $16,314 – 65,682 (1998 USD) Average Medicare payments among patients with SCCHN were $25,542 higher than those of matched comparison group (p<0.001) (1998 USD)	Advanced SCCHN patients had shorter survival and higher costs than patients diagnosed as having distant, regional, local and in situ cancer. Medicare looks at patients >65yrs. Data 1991 to 1993	Not mentioned in report. ICD-9 codes used to identify patients. Possible to separate by HPV-associated subsites.

Abbreviations: CPT-4: Current Procedure Terminology codes; HNC: Head and neck cancer; ICD-9: International Statistical Classification of Diseases and Related Health Problems 9th Edition; OSCC: Oral squamous cell carcinoma PPO: Preferred Provider Organization; SCCHN: Squamous Cell Carcinoma of the Head and Neck. USD: United States Dollar.

Discussion

The first observation about the studies reviewed in this chapter is how heterogeneous HNC patients are. The variations in the studies are most likely due to the context of the research question and the nature of the data source. The most notable feature is that HPV is not mentioned in any of the cost studies (Table 4). Therefore, there is nothing to infer about the cost studies of HPV-related HNC other than the review suggests a long time lag between clinical and economic studies. A major improvement in characterising the economic burden of HPV-related HNC (in the US or anywhere else) would be recognition that this cancer is distinct from other types of HNC. Without ICD codes indicating to an analyst that a patient has HPV-positive HNC, the *de facto* situation will be the reference to HPV-associated HNC sites adjusted by percentage that are HPV-positive from other studies, which is the case with the two studies in Table 3. The reality on the ground is that HPV testing of suspected HNC is not even routinely done in many clinical institutes. A JHMI study used fine-needle aspirations (FNA) of neck metastasises from suspected primary oropharyngeal tumours to determine HPV status which would make it easier for clinicians to diagnose HPV-related HNC (Smith et al., 2014). [23] Therefore, it seems that it will be a long time before registries collect this type of information.

The second observation is regards the subjective nature of the methods used in economic burden studies. In this review of HNC studies and in general, a specific research question is posed from a certain perspective which often predicates the methods employed and directs the researcher

[23] This study was designed to facilitate widespread testing for HPV in HNC. The study involved ascertaining a sample of tissue by FNA from a suspected lymph node metastasis (neck area) and analysing using a hybrid capture (HC-2) assay. The same assay used in HPV-related cervical cancer. The estimated cost savings of FNA rather than standard care to the government payer (i.e. Centers for Medicare and Medicaid Services) ranged from $113.74 to $364.63 per patient (Smith et al., 2014).

to particular data sources or alternatively, predicated on what data is available; numerous variations in estimation procedures are employed. These methods are commonly categorised into either a 'top-down' (population-based) or 'bottom-up' (person-based) approach (Hodgson and Meiners, 1982).[24] The components that are included are also subjective and linked to the perspective taken at the outset of the study. Ekwueme et al. (2008) wanted to estimate the societal mortality-related burden (in terms of YPLL and productivity costs) of HPV-associated cancers (without regard to the percentage of each of these cancers that could be attributed to HPV) and all malignant cancers in the United States in 2003 (Ekwueme et al., 2008). The purpose of the study was to estimate the scale of HPV-related cancer and compare between sites. This study is probably the most informative to a public policy-making and puts an annual figure of $1.37bn on the total mortality costs using a human capital approach {Other options are (i) friction costs associated with the cost to employer in replacing the sick individual or (ii) a willingness-to-pay (WTP) approach which determines the value of life based on a person's WTP for small reductions in the probability of dying}.

The third observation from this review is that the disease-specific estimate does raise methodology concerns – specifically the 'adding-up' constraint which is when it is not entirely clear to the analyst what costs are associated with which disease, and how to ensure that all medical spending is allocated to one and only one disease (Clabaugh and Ward, 2008). Le et al. (2011) refer to the 'any-cause total healthcare costs' which is likely to be substantial greater than the 'disease specific' costs. For analysts using retrospective datasets, attribution of costs to a particular

[24] A retrospective 'bottom up' microcosting study using data from GBMC attempted to compare healthcare utilisation of those with HPV-positive HNC to HPV-negative HNC. As noted about any microcosting study, substantial requirement is needed for coordination to collect detailed resource utilisation data (Frick, 2009), which makes them difficult to perform adequately.

disease can be very difficult especially if the patient has a number of other medical conditions. This issue is revisited in the next chapter.

Despite the growing popularity of economic burden/COI studies in the US (Akobundu et al., 2006), there is little published guidance to support the choice of methodological approach to be used. Many COI in the US are not comparable as they differ in terms of valuation approaches used, perspective adopted and components of care analysed (Clabaugh and Ward, 2008). As a criticism, large 'cost' estimates may simply be one-upmanship by disease advocates vying for greater funding (Reuter, 2006). The positive aspects of COI studies are that they draw the public's attention to particular health problems and encourage policy debate, they may also inform planning of healthcare services, the prioritisation of prevention research and the evaluation of policy options (Rice, 2000)(Rice, 1994)(Finkelstein and Corso, 2003). In some cases, COI estimates are broken down to show the distribution of disease costs across healthcare services and payers, which can help demonstrate the burden borne by specific stakeholders (Finkelstein et al., 2003). In HPV-related HNC, there is likely to be substantial survivorship burden, implied by the epidemiological statistics, which are not captured in these studies. One very important nuance illustrated by the Hu and Goldie (2008) study was that they estimated the 'total lifetime costs' for new cases of HNC. This distinguishes the difference between prevalence and incidence costing methods and their uses. Hence, the estimate is suitable as a lifetime cost value for CEA models.

COI OF HPV-related HNC in the US

An attempt to summarize the COI components of HPV-related HNC in the US has been described in Table 5. The Table contains the pertinent estimates that have been extracted from the literature that describes the COI by the 'societal perspective' (Table 2).

Table 5: Characterising the cost-of-illness of HPV-related HNC in the US

Components to characterise the cost of illness	Authors	Notes
Direct Medical Costs	NCI, 2014	All HNC: $3.64bn per year (2010 USD) • Initial care ($1.08bn; 29.7%) – The first 12 months after diagnosis • Continuing care ($1.01bn; 27.7%) – Time between initial and last year of life • Last year of life ($1.55bn; 42.6%) – The final 12 months of life
	Chaturvedi in Aldestein et al. 2009	HPV-related oropharyngeal cancer: $151million per year (2003USD)
Cost per Case	Hu & Goldie 2008	Oropharyngeal and mouth cancer: $33,020 (2003 USD) is the average discounted lifetime cost per case HPV-related oropharyngeal and mouth cancer – Total discounted lifetime cost for HNC in 2003 is $38.1m (Range: $17.7- 54.1m)
Indirect medical costs	n/a	No estimate of these costs have been reported
Productivity losses	Bradley et al. 2008	All HNC: $3.6bn (2010 USD) – PVLE among adults ≥ 20years in 2010 based on 12,109 deaths
	Ekwueme et al. 2008	HPV-related HNC sites: $1.37bn (2003 USD)
Intangible costs	n/a	No estimate of these costs have been reported

Abbreviations: n/a: not available, HNC: Head and Neck Cancer, HPV: Human Papilloma Virus, PVLE: Present value of lifetime earnings; USD: United States Dollars

A nationally representative longitudinal cohort study of HNC patients with controls would be the design of the ideal economic burden study. It would capture the direct medical expenditures (using a unique identifier), patient's employment status and quality of life from diagnosis to death. However, such a study is unrealistic and would be too expensive to fund. Social scientists and economists currently work with datasets that capture specific data over a shorter timeframe. The MEPS is an example of a data source that is used to estimate the direct medical expenditures of a disease and combined with Bureau of Labor wage rates, assign productivity losses with assumptions. As will be discussed in the next chapter, even then a variety of statistical methods and approaches can be used to estimate the direct medical expenditures.

Conclusion

This review highlights that HNC patients are a heterogeneous group and an appreciation for the HPV link is not evident in the economic burden literature in the US. The context, perspective, and the methodology used to arrive at the economic burden estimate varied considerably between studies.

Reference:

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Clabaugh, G., Ward, M.M., 2008. Cost-of-illness studies in the United States: a systematic review of methodologies used for direct cost. *Value in Health*, 11, 13–21.

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Chapter 4: Comparison of Direct Medical Expenditures Estimation Methods of Head and Neck Cancer

In this chapter, the methodological challenges in estimating the direct medical expenditures (or 'medical costs') component of a COI study for HNC is examined. The data source used to conduct the analyses in this chapter is the US nationally representative Medical Expenditure Panel Survey (MEPS) - A commonly used source for estimation of the burden of various diseases (Cohen et al., 2009). Following on from chapter 3, it is the prevalence cost of a disease for a specific calendar year for all individuals diagnosed with or living with the disease that can be estimated using MEPS. Previous economic studies of HNC in the US were derived from non-nationally representative sources - SEER-Medicare (Lang, 2004) and managed-care population (Amonkar et al., 2011). As has been demonstrated with colorectal cancer, considerable variability across different datasets in estimating prevalence costs exists (Yabroff et al., 2009). [25]

The specification of what constitutes 'cost' is important to consider. There is universal agreement that the cost of any healthcare activity should be defined in terms of the 'economic opportunity costs' of the component resources, with each resource valued in its next best use (Lipscomb et al., 2009). However, in costing studies, the definition of 'cost' can be either 'charges' or 'prices' obtained from providers or 'expenditures' reimbursed by payers. The difference between charges and costs is illustrated by Health Care Utilization Project (HCUP) data for HNC (Table 6). Mean 'charges' for inpatient admission are about 3 times mean 'costs' for HCUP data. [26]

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[25] The prevalence cost estimates (mean net annual per person in $2004) for patients with colorectal cancer in the SEER-Medicare were $5,341 (95% CI: $5,243, $5,439), compared with $8,736 (95% CI: $8,203, $9,269) for the Medicare claims only and $11,614 (95% CI: $7,566, $15,663) for the MEPS.

[26] In HCUP, Cost-to-Charge ratios are used to estimate the resource cost of inpatient care and its variation across hospitals and conditions. Costs tend to reflect the actual costs of production, while charges represent what the hospital billed for the case.

Table 6: Charges and costs associated with HNC inpatient stays (National Inpatient Sample, 2010)

		Total Number of discharges		Length of stay (LOS), days (mean)	Charges, $ (mean)	Costs, $ (mean)	Aggregate charges, $ (The "national bill")
All discharges		33,603	100.00%	7.5	65,150	19,934	2,192,427,849
Payer	Medicare	14,517	43.20%	7.8	67,742	20,366	985,364,640
	Medicaid	5,355	15.94%	9.7	69,846	22,151	374,097,248
	Private insurance	10,384	30.90%	6.1	61,730	18,539	642,376,206
	Uninsured	1,842	5.48%	8.1	54,299	18,675	100,012,675
	Other	1,468	4.37%	7.0	61,265	19,229	89,947,709
	Missing	*	*	*	*	*	*

The motivation for this chapter is that in characterising the economic burden of HNC, a policy-maker ought to have an appreciation for the various methodologies used to produce these estimates. To inform policy, it is also important that an analyst portray what the costs are (in terms of healthcare utilisation, which will be further discussed in chapter 5) and where they fall (who pays). In the US, MEPS is an appealing data source for analysts intent on informing public policy. MEPS can link information on individuals and households to their use of and expenses for healthcare (Clabaugh and Ward, 2008). The standardized metric of 'cost' used in MEPS is the actual dollar amount paid for medical services (i.e. actual payments to providers of the healthcare). Chapter 4.1 will provide more detail on MEPS.

Objective

The objective of this empirical work is to compare and contrast the different approaches to the estimation of direct medical expenditures associated with HNC in the US using the MEPS dataset. This study

Total charges are converted to costs using cost-to-charge ratios based on hospital accounting reports from the Centers for Medicare and Medicaid Services (CMS). Source: http://www.hcup-us.ahrq.gov/reports/methods/2008_04.pdf (accessed: 7th April 2014)

design allows for exploration and discussion of each approach. The following sections of this chapter are: A brief commentary on the data source, a literature review of MEPS costing studies from 2005 to 2012, implementation of four different estimation approaches identified in the literature, discussion of econometric issues and concluding thoughts on using this data in discussing the economic burden of HNC and evaluation of gender-neutral HPV vaccination.

4.1 The Medical Expenditure Panel Survey

The growing demand in the US for accurate and reliable information on the population's healthcare utilisation, expenditures, insurance coverage, sources of payment, and access to care, served as the catalyst to initiate the family of national medical expenditure surveys sponsored by the Agency for Healthcare Research and Quality (AHRQ) and its predecessor agencies. AHRQ's MEPS, cosponsored by the CDC's NCHS, collects detailed information regarding the use and payment for healthcare services from a nationally representative sample of Americans (Cohen et al., 2009).

The MEPS consists of a family of 3 interrelated surveys: the Household Component (HC), the Medical Provider Component (MPC), and the Insurance Component (IC). The MEPS household sample, which provides the basis for HC and MPC data collection, is selected from participants in the previous year's National Health Interview Survey (NHIS). For example, the HC sample size in 2009 was 13,875 families and 34,920 individuals.[27] MEPS-HC consists of an overlapping panel design in which any given sample panel is interviewed a total of 5 times in person over a fielding period of about 30 months. This yields annual health insurance coverage, use and expenditure data for 2 calendar years. The interview is administrated through a computer-assisted personal interview (CAPI) loaded onto a laptop computer, and takes place with a knowledgeable family respondent who reports for him or herself and for other family members.

The MEPS-MPC is a supplement to the household component. It is designed to provide additional information on charges and sources and amounts of payment received by providers for care reported by household respondents. For the MPC, permission is obtained to collect information directly from the providers used by participants in the

[27] As stated in a presentation on the 15th September 2011 at the AHRQ's workshop in Rockville, Maryland on using MEPS

household survey, and those providers are contacted separately for charge and payment data associated with the event. The MPC sample for 2006 consisted of approximately 5,500 hospitals, emergency rooms and outpatient departments, 12,000 office-based doctors, 7,500 pharmacies and 600 home care agencies used by MEPS sampled persons. In addition, the sample contained about 13,000 separately billed physicians who provided care associated with reported hospital events (Cohen et al., 2009). Response rate for the MPC are high, ranging from about 80% for pharmacies to more than 90% for hospitals. Because the provider reported data are more reliable, they are used to construct the MEPS expenditure variables (Cohen et al., 2009).

The MEPS is the only source of nationally representative data on individuals' use of and expenses for medical services, which are linked to specific conditions. Information on specific medical conditions is obtained in the MEPS interview by asking respondents which 'health problems' had 'bothered' each household member during the observation period. Also, respondents reported the reason for each medical event. This method identifies HNC respondents that result in an estimate of the annual 'treated prevalence'. This would be distinct from incidence (establishing phase-of-care expenditures) and prevalence (which includes long-term survivors expenditures) cost-of-care estimates.

Limitations

The survey does not include people incarcerated, in the military or in nursing homes. Because utilisation estimates from the survey are based on household reports there is some underreporting of individuals' medical events. Household respondents are subject to misreporting because of a lack of specific technical knowledge.

Because of confidentiality concerns, ICD-9 conditions in the public use files are reported only at a 3-digit level of specificity, rather than the

full 5-digit level which is insufficient to identify HPV-related HNCs (only ICD codes that recognise HPV as a causal agent can truly be accurate). In addition, much of the condition related research conducted using the MEPS is based on aggregations of conditions, as developed by AHRQ in the Clinical Classification Software (CCS) system. The CCS is a tool for clustering 17,000 ICD-9 condition codes into 285 mutually exclusive and homogeneous categories that are more tractable for analytic purposes (HCUP, 2012). However, research has indicated that condition reporting in MEPS is most salient to individuals because they involve ongoing treatment, prescribed medications, or lifestyle changes. Thus, MEPS can support many, but not all types of condition analyses.

4.2 Literature Review of MEPS Expenditure Estimation Studies

MEPS is a popular data source for COI studies (Honeycutt et al., 2009). Staff at AHRQ, have previously discussed methodological issues related to estimating the COI of diabetes (Olin et al., 2008) and obesity (Rhoades, 2006). Given the lack of strict COI guidelines in general and when using MEPS, a literature review of recent MEPS studies (2005-2012) was undertaken to instruct the estimation methodology and to describe the variability that exists between different published reports.

The specified lower cut-off date of 2005 is because in 2006, systematic review by Akobundu et al. (2006) of COI studies suggests a typology to describe the direct medical expenditures of any disease. Four distinct COI estimation methods were identified along with a proposed gold standard (Table 7). The distinction between total and incremental expenditures is very pertinent, which will be described later in relation to the empirical analysis of HNC.

Table 7: Description of cost-of-illness studies (Akobundu et al. 2006)

Cost-of-Illness Method	Brief Description
Total Expenditures:	
1. Sum All Medical	Identify all patients with a diagnosis and sum costs
2. Sum Diagnosis Specific	Identify all patients with a primary diagnosis and sum costs for treatments for that diagnosis
Incremental Expenditures:	
3. Matched Control	Identify all patients with a diagnosis and sum costs. Subtract out the average cost of the sample to find incremental costs for treatment; alternatively, subtract out the average cost of a matched cohort instead.
4. Regression	Identify all patients with a diagnosis, complete a regression analysis and indicate the individual β for each diagnosis
Gold Standard – Identify all patients with a diagnosis, find a matched cohort and complete a regression analysis to quantify the individual β for each diagnosis	

This review of the MEPS literature pertains to studies that report healthcare expenditure estimates. The following search terms were used: In PUBMED: ('methods' [MeSH Terms] OR 'method' [Text Word] OR 'Economics' [Mesh]) AND ('Medical expenditure panel survey' OR 'MEPS') and EMBASE: ('cost analysis'/exp OR 'cost analysis' AND 'Medical expenditure panel survey'). Other databases searched were: Econlit, Web of Science and Tufts CEA Registry. The inclusion criteria consisted of articles that reported an annual per-respondent direct medical expenditure for a specific disease or condition between 2005 and 2012. The final searches took place in January 2013. The information elicited from available papers included the following: Direct medical expenditure estimate method, model specification/diagnostic tests, comorbidity measure, MEPS data files used and description of economic study in title of paper.

The results are illustrated by a PRISMA flow diagram (Figure 14) that highlights the identification, screening and eligibility stages of conducting a literature search (Moher et al., 2009). [28]

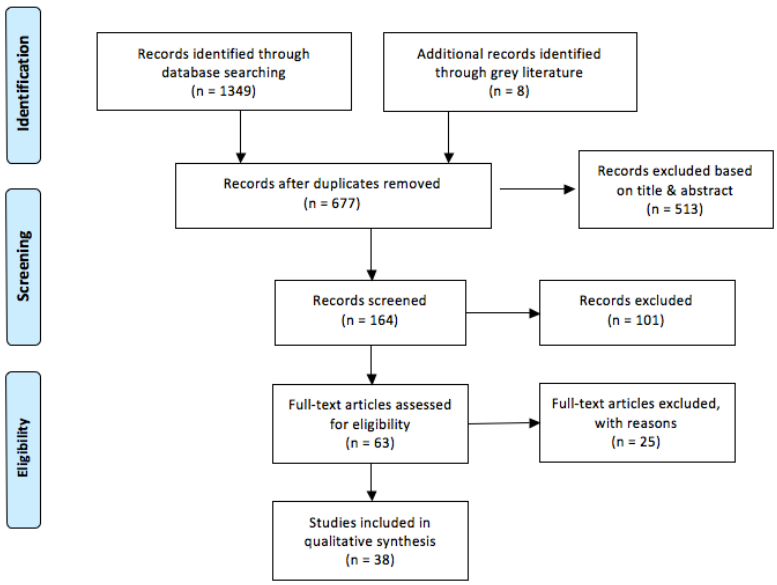

Figure 14: PRISMA reporting of literature review search of MEPS direct medical expenditure studies

[28] http://www.prisma-statement.org/ - PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Minimum set of items for reporting.

After an examination of sixty-three articles that could have potentially included data on methods and expenditure estimation, thirty-eight studies met the inclusion criteria. The pertinent points raised from the review were that:

- None of the previous MEPS healthcare expenditure studies in the review reported a range of estimates using all four COI methods.
- Only eight studies reported estimates using more than one of these methods.
- Regression models were the most popular method (31/38) of estimating the effect of a condition on healthcare expenditures.
- Five studies reported disease-specific expenditures.
- Two studies used disease-related events to identify patients
- Three studies used just a matching approach
- Five studies reported the summation of all medical expenditures associated with a disease approach.

There was considerable methodological heterogeneity among the regression models. For just positive expenditures, the generalized linear model (GLM) log link and gamma distribution was the most popular with twelve studies followed by the logarithm of expenditures in an ordinary least squares (OLS) regression with nine studies (Studies are identified in appendix at the end of this chapter as 'GLM' and 'LOG').

AHRQ personnel (Hill and Miller, 2010) compare various regression approaches including the Generalized Gamma and the Extended Estimating Equation (EEE) approach. They found that Basu and Rathouz's EEE model (Basu and Rathouz, 2005), which has a flexible link function, is a robust estimator that performs well over different data distributions. More sophisticated methods have included using instrumental variables in estimating the medical care costs of obesity

(Cawley and Meyerhoefer, 2012) and what Akobundu et al. (2006) describe as the 'gold standard' approach of combining matching and regression in asthma (Rappaport and Bonthapally, 2012).

As a matter of reliability, analysts should provide an explanation of why they did what they did methodologically. Of the GLM regression studies, only eight made reference to model specification and diagnostic tests (Studies are identified in appendix at the end of this chapter as 'Tests'). As for the consistency indicator of whether analysts accounted for comorbidities, twenty-six studies did account for comorbidities or made some type of risk adjustment (Studies are identified in appendix at the end of this chapter as 'COM'). Such methods included accounting for specific medical conditions, creating a count of chronic diseases or using the Charlson Comorbidity Index (CCI). On the other hand, it has also been argued that theoretically comorbidities should be equally prevalent in populations of people with and without certain stand-alone diseases (Martin et al., 2009).

This literature review also highlighted the variation in the description of the title of MEPS cost studies - 'Medical expenditures', 'incremental cost analysis', 'treatment cost', 'economic burden' and 'health services expenditures and utilisation'. Variation was also seen in the description of MEPS data files that were used – 'Medical conditions file linked to the consolidated expenditure file', 'event files merged with consolidated population file' and 'medical conditions file and event were merged with full-year consolidated files'. The vague descriptions of files used and steps taken make it difficult for other analysts wanting to replicate these studies based on the descriptions in peer-reviewed publications. In conclusion, this literature review highlights issues with: 'validity' of estimation methods used; the 'reliability' of the models in the absence of specification tests and the lack of 'consistency' in accounting for comorbidity. The review also shows the original contribution to the literature that this empirical analysis of HNC adds by reporting and discussing the four outlined methods.

4.3 Direct Medical Expenditure Estimation of Head and Neck Cancer

In the MEPS data files, International Classification of Disease - ninth version-Clinical Modification (ICD-9-CM) condition and V codes that have been aggregated for each clinical classification category. For HNC, the CCS is number 11 and contained 85 separate ICD-9-CM or V codes (See appendix, p.223). As the annual number of cases of HNC in the MEPS is smaller than the 100 observations that AHRQ suggests for making national estimates, 6 years of data (2003-8) were pooled to generate an analytic sample (Yu and Machlin, 2004). In this case, the 'pooled weight' is the yearly person weight divided by number of years (i.e. six). All expenditures were inflation adjusted to 2008 dollars using the medical component of the Consumer Price Index.[29] MEPS pooled data produces 'average annual' estimates based on 'person-years'. This is because the same respondent can be observed in 2 years of consolidated year files. Total expenditures for a medical event are defined as the sum of direct payments made by all payers.

Data Files

With MEPS, there are a number of different types of public use files (PUF) available to analysts. They are stratified at person-level, medical event-level, condition-level and job-level.[30] For each year, MEPS also produces a consolidated full year data file that contains expenditure and utilisation ('event') data for the calendar year from several rounds

[29] The Consumer Price Indexes (CPI) program produces monthly data on changes in the prices paid by urban consumers for a representative basket of goods and services - http://www.bls.gov/cpi/ (accessed 7th April 2014) – However, MEPS recommend that the Personal Health Care Expenditure inflation index be used when pooling expenditure data. This was an oversight on my part. I used the CPI index as it was the most common inflation index used in the literature review. http://meps.ahrq.gov/mepsweb/about_meps/Price_Index.shtml (accessed 7th April 2014)

[30] This file contains jobs level information and includes variables pertaining to household-reported jobs, including wages, hours, industry, and occupation.

of data collection. The event files contain data for the calendar year on the following unique household-reported medical events:

- Office-Based Medical Provider Visits File
- Prescribed Medicines File
- Emergency Room Visits File
- Hospital Inpatient Stays File
- Other Medical Expenses (Home health visits)

Healthcare expenditures are collected at the event level. They represent payments to providers of the healthcare service. Payments are reported by source (e.g., out-of-pocket, private insurance, public program). The 'total expenditure' variable in the consolidated full year file is the sum of payments across all sources. Expenditures are derived initially from MPC and if not available from HC. Events with no MPC or HC data on expenditures are imputed which results in no missing data. This is achieved through a weighted hot-deck imputation procedure (Cox, 1980), with data from the MPC used as the primary donor source wherever possible. In general, the hot-deck procedure sorts donor events (complete data) and recipient events (missing data) into imputation cells based on important predictors of expenses available in MEPS.[31] The 'condition-link' file enables events and condition files to be linked using the 'DUPERID' variable.

Statistical Software

SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) and Stata 11.2 software (StataCorp, College Station, Texas, USA) were used for statistical analyses. The analyses incorporated MEPS person-level weights and variance adjustment weights (strata and primary sampling unit) that yield nationally representative estimates.

[31] http://meps.ahrq.gov/data_files/publications/mr19/mr19.shtml#Imputation (Accessed: 11th May 2014)

Approach 1: Sum Medical Expenditures on those with condition

In this approach individuals with the condition are identified and the sum of their medical expenditures estimated. In MEPS, this is achieved by using the consolidated full year file and the condition file. Then, this yearly file is combined with other yearly files to give the pooled dataset. The *'treated prevalence'* is considered as being those who have a diagnosis of HNC with any medical event. This is considered to be the middle ground between respondents who have reported a diagnosis of HNC without necessarily any medical events and those with HNC-specific medical events, who have been referred to as *'affected prevalence'* in a study on cancer survivors (Short et al., 2011). This method is straightforward but provides an estimate of all expenditures with HNC rather than isolating the expenditures specifically due to the disease; this will certainly overestimates expenditures attributable to HNC.

Approach 2: Sum Disease-Specific Medical Expenditures (Attribution) on those with condition

This method restricts its attention to medical expenditures related to the disease of interest. In MEPS, this is achieved by using the consolidated file, the condition file, condition-event link and events files including inpatient, emergency room, outpatient, office-based, home health and pharmacy. Then, this yearly file is repeated for each year and pooled. A HNC 'case' is defined as an adult with a HNC (CCS=11) specific medical expenditure. [32] This method may underestimate the direct medical expenditures as it fails to include 'spillover costs' attributed to a specific condition. An example of a 'spillover cost' in cancer care would be a doctor visit for chemotherapy-induced nausea, which will be coded as nausea and therefore unknown to the analyst to be cancer-related (Howard et al., 2004). Undoubtedly, other medical expenditures (e.g. mental health

[32] This is based on two workshops at AHRQ, Rockville, MD in May and September 2011 on how to use MEPS data effectively.

issues) may also be attributed to a respondent's cancer. Given that the absence of reliable epidemiologic estimates in the literature, it was decided not to attribute any expenditure fraction of other conditions to HNC, which rules out 'double counting' - Coding of MEPS medical events might be associated with more than one condition and without accounting for this duplicating of expenditures can occur. [33]

Approach 3: Incremental Expenditures by Matching Methods of those with and without the condition

A case-control matched analysis is often used in observational studies to reduce selection bias and approximate a randomised trial. The objective of matching is to find an observation (control) that is as similar as possible on the observed covariates to the observation that has the HNC (case). [34] That is to say that cases and controls have similar covariate distributions – e.g. percent women would be 'balanced' among cases and controls. Matching variables should be related to the condition (e.g. HNC – more likely to occur in men, therefore sex would be an important variable to match on) and the outcome (e.g. Total medical expenditure – insurance status would be important variable to match upon) (Stuart, 2010). This is done in MEPS on the pooled dataset outlined in approach 1. There is little guidance/consensus on how to specifically implement matching analyses with total expenditure as the dependent variable. The general advice is to think carefully about the set of covariates to include in the matching procedure, and err on the side of including more rather than fewer (Stuart, 2010). As expenditures are payments, covariates that may be related to a respondent's ability to pay for treatment should be included in the matching algorithm. Inherently, this approach

[33] In MEPS, one event can be associated with more than one condition. I kept all events associated with HNC even if linked to another condition.

[34] Matching methods attempt to replicate two features of randomized experiments - Create groups that look only randomly different from one another (at least on observed variables) and doesn't use outcome when setting up the design. Matching is a common method of adjustment in observational studies. Matching helps to address many confounder-related distributional imbalance problems at the design stage of a study rather than at the analysis stage.

introduces a degree of subjectivity into the estimate (no more so than what should be included in a multivariate regression).

The matching variables used in the reported analyses are age, sex, race, insurance status (proxy for ability to pay), number of priority medical conditions (proxy for co-morbidity), and year of data collection.[35] All variables were given equal weight. To ensure that a full 1:1 match was achieved, up to 7-year age gap between cases and controls was allowed. However, the legitimacy of using survey population weights in making national estimates is debatable with arguments existing around whether weights are meaningful in the context of matched samples (Lurie et al., 2009). If the aim of the study is to make population level (rather than survey sample) estimates, then survey weights are important to incorporate into the model (See discussion for more on this interesting point).

GMATCH (Kosanke and Bergstralh, 2004), a nearest neighbour matching routine without replacement (controls only allowed to be used as a match once) in SAS is commonly known as 'Greedy Matching' was used in this analysis. GMATCH goes through the cases one at a time and picks the best control match based on defined characteristics. The first step is identifying which control is 'best' for a particular case. This can be determined using a distance measure, $D_{ij,}$ between the i^{th} case and j^{th} potential control. The greedy algorithm sorts the cases and the controls randomly and matches the first case with the closest control using the smallest D_{ij}, and repeats the process until all cases are matched.[36] The mean total expenditure of the controls is then

[35] The Priority Conditions section of the MEPS-HC questionnaire, added in 2000, collects information about a select group of medical conditions including sore or strep throat, diabetes, asthma, hypertension, coronary heart disease, angina, heart attacks, other heart disorders, strokes, emphysema, joint pain, and arthritis. MEPS collect information about this select group of medical conditions that have been specified by the Agency for HealthCare Research and Quality as 'priority conditions'. http://meps.ahrq.gov/mepsweb/data_stats/MEPS_topics.jsp?topicid=41Z-1 (accessed: 7th April 2014)

[36] Let $X^1 = \{x^1_{1,}x^1_{2,}x^1_{3,} \dots \dots, x^1_p\}$, and $X^0 = \{x^0_{1,}x^0_{2,}x^0_{3,} \dots \dots, x^0_p\}$ be the vector of matching variables for N cases and M controls (M ≥N). Then, one possible definition for D_{ij} is

subtracted from the mean total expenditure of the cases to give the estimated mean incremental expenditure. This is then multiplying by the sum of the survey weights of the cases to give a national estimate of the 'annual average' economic burden of HNC.

Approach 4: Incremental Expenditures by Regression-Based Methods

The Andersen conceptual model of health services utilisation is a popular organizing framework (Andersen, 1995). An example of a MEPS study that uses this model looks at serious psychological distress (Dismuke and Egede, 2011). The model suggests that an individual's utilisation of healthcare services is a function of predisposing (e.g. age, gender, race/ethnicity, education), enabling (e.g. poverty category, insurance, region) and need (e.g. self reported health status, number of priority chronic conditions, smoking status) factors (See figure 18 in chapter 5 for more details of the Andersen model, p.118).

Healthcare expenditures pose particular challenges for econometric modelling. The distribution of strictly positive expenditures is typically skewed, kurtotic and heteroskedastic (Blough et al., 1999).[37] A variety of models have been used to analyse expenditure/cost data with many analysts now presenting more than one model in their reports (Basu et al., 2006)(Hill and Miller, 2010). The most popular MEPS regression model from the earlier literature review (chapter 4.2) was the GLM method and is reported here. Increasingly, GLM is a popular approach to modelling healthcare expenditures but not without its limitations (Basu and Manning, 2009). The GLM framework requires a link function that relates the conditional mean to the covariates and a

based on the weighted sum of the absolute difference between the *i*th case and the *j*th potential control, i.e., $D_{ij} = \sum_{k=1}^{p} |x_{ik}^{i} - x_{ik}^{0}| \times W_k$ and the total distance $T = \sum_{i=1}^{N} D_{ij}$ is thus a natural way to evaluate how well the entire group of cases is matched to the controls. Source: http://www2.sas.com/proceedings/sugi29/208-29.pdf (accessed; 7th April 2014)

[37] The relationship between costs and covariates may be nonlinear in models of expenditure data and errors may exhibit substantial heteroskedasticity (Jones et al., 2013) This is handled in the GLM framework by modelling the variance as a function of the conditional mean.

distribution, to specify the relationship between the variance and the mean (Manning and Mullahy, 2001). The most popular specification of the GLM for healthcare expenditures has been the log-link (Eqn. 1) with a gamma distribution (variance proportional to the square of the mean; λ=2 in Eqn. 2) (Jones et al., 2013).

$$E[y \mid x] = f(x'\beta) = \exp(x'\beta) \ln(E[y \mid x]) = x'\beta \quad (1)$$

$$y \sim Var(y \mid x) \approx (E[y \mid x])^{\lambda} \quad (2)$$

The specification and diagnostic tests used in this analysis came from the 'glmdiag' program.[38] This Stata user program performs the recommended modified Park test[39] for the GLM family and the Pearson correlation test (checks for systematic bias in fit on raw scale), the Pregibon link test[40] (checks linearity of response on scale of estimation), and the modified Hosmer and Lemeshow test[41] (checks

[38] General Internal Medicine | University of Pennsylvania Health System, 2011. http://www.uphs.upenn.edu/dgimhsr/stat-cstanal.htm (Last accessed 19/1/13).

[39] The rationale that underlies this test is that it uses the residuals and predictions on the untransformed scale for costs to estimate and test a very specific form of heteroscedasticity – one where the raw-scale variance is a power function of the raw-scale mean function. Manning and Mullahy (2001) state that the idea behind the test is based on the variance function being proportional to the conditional mean. The Park test exploits the relationship by using a regression of $\ln(y_i - \hat{y}_i)^2$ and $\ln(\hat{y}_i)$ and a constant, where $\hat{y}\,i$ is obtained from a preliminary GLM regression.

[40] To test the reliability of the specification of a model - Pregibon's link test is widely used as an alternative to the Regression Equation Specification Error Test (RESET). The test adds the level of the fitted values (and its square) rather than including the individual regressors and consists of testing the null hypothesis that the coefficient of the square of the fitted values is not significantly different to zero – In Stata – linktest command (Jones et al., 2013).

[41] For nonlinear regression models, the link test for misspecification of the regression model may be augmented by a modified Hosmer and Lemeshow test and its variants. The idea is to compute the fitted values and prediction errors for the model on the raw cost scale. These prediction errors can then be regressed on the fitted values, testing whether the slope equals zero (Jones et al., 2013). If the coefficients of the nonlinear regression model are increasing with the deciles of the fitted values, rather than being a random scatter around zero, this suggests that the model over-predicts or under-predicts and the exponential conditional mean is not well specified.

for systematic bias in fit on raw scale) for the GLM link (Glick and Doshi, 2011). These tests jointly assess how well the model fits the data. The incremental expenditures were calculated by the method of 'counterfactual regression predictions' (or sometimes called recycled predictions) which gives an incremental expenditure figure based on the difference between the entire sample having HNC and no respondent having HNC (Jones, 2011). The incremental expenditure estimate is then multiplied by the pooled population weight to give the national estimate of direct medical expenditures.

The alternative regression-based approach uses the user written program pglm to run the EEE model. The EEE approach estimates the link and variance functions directly using the available data and thereby avoids many of the problems due to misspecification. The model makes use of the Box-Cox transformation for the link function:

$$x_i\beta \;=\; \{\; \frac{\mu_i^{\lambda}-1}{\lambda} \qquad if\ \lambda \neq 0$$

$$\log(\mu_i)\ \ if\ \lambda = 0 \quad \text{where } \mu_i = \mathrm{E}[y_i \mid x_i]\}$$

This is complemented with a general power function specification for the variance:

$$var(y_i \mid x_i) = v_1\mu_i^{v_2}$$

This allows restrictions corresponding to common distributional family types to be directly tested, for example v_1 =1; v_2=1 corresponds to a Poisson distribution and $v_1 > 0$; v_2=2 the gamma distribution.

An alternative is to specify a quadratic function of the variance:

$$var(y_i \mid x_i) = v_1\mu_i + v_2\,\mu_i^2$$

which corresponds to the Poisson distribution when $v_1 = 1$ and $v_2 = 0$ and the gamma when $v_1 = 0$ and $v_2 > 0$ (Jones et al., 2013).

The biggest advantage with EEE is that the analyst is not required to know the appropriate link or distributional family. The relevant parameters defining the link and variance function are estimated via ancillary estimating equations. The regression approach is on the pooled dataset outlined in approach 1.

Results - Analytical Sample

The annual number of respondents that self-reported to have HNC in the MEPS dataset (12-30 per year, pooled =120) is small relative to the number of people in the survey (~30,000 per year, pooled=191,407). To consider the *'treated prevalence'*, the characteristics of the respondents that had a medical expense in a given year were examined. There are 82 distinct individuals that sum to 113 *'person-year'* cases (This is because the same respondent can be observed in 2 years of consolidated year files). Of these only 2 cases were children. The focus is on adults because children are likely to have a different comorbidity profile than adults and this may impact the resource use and expenditure (Ogle et al. 2000). This left 111 *'person-year'* cases in our analytic sample (see Table 8).

Table 8: Comparison of demographic characteristics in MEPS adult respondents with and with Head and Neck Cancer (2003-2008)

	Head and Neck Cancer (N=111)	General Adult Sample (N=131,041)
Age, Mean (se), years	63.21 (1.11)	46.16 (0.05)
Gender (%)		
Male	76 (68%)	59,850 (46%)
Female	35 (32%)	71,191 (54%)
Race (%)		
White	89 (80%)	100,338 (77%)
Black	18 (16%)	20,922 (16%)
Asian	3 (3%)	6,261 (5%)
Other	1 (1%)	3,520 (3%)
Ethnicity (%)		
Hispanic	6 (5%)	31,019 (24%)
Non-Hispanic	105 (95%)	100,022 (76%)
Education		
No Degree	29 (26%)	31,062 (24%)
GED/HS Diploma	56 (50%)	63,609 (49%)
Bachelor Degree	26 (23%)	35,608 (27%)
Employment		
Not Employed	67 (60%)	43,966 (34%)
Employed	39 (35%)	85,451 (65%)
Poverty		
Poor	22 (20%)	21,841 (17%)
Near Poor	10 (9%)	7,825 (6%)
Low Income	16 (14%)	21,108 (16%)
Middle Income	26 (23%)	38,541 (29%)
High Income	37 (33%)	41,726 (32%)
Metropolitan statistical areas (MSA)		
Non-MSA	25 (23%)	23,185 (18%)
MSA	81 (73%)	106,502 (81%)
Region		
West	17 (15%)	33,987 (26%)
Northeast	13 (12%)	19,788 (15%)
Midwest	22 (20%)	25,794 (20%)
South	54 (49%)	50,118 (38%)
Health Insurance		
Uninsured	1 (1%)	24,905 (19%)
Public only	50 (45%)	80,433 (61%)
Any private	60 (54%)	25,703 (20%)
Self-Reported health status		
Poor/ Fair		
Good/V.Good/Excellent	49 (44%)	20,334 (16%)
Not ascertained		
	50 (45%)	108,863 (83%)
	12 (11%)	1,844 (1%)
No. of Priority Chronic Condition		
0	30 (27%)	71,469 (55%)
1-2	46 (41%)	45,327 (35%)
3-5	25 (23%)	12,872 (10%)
6+	10 (9%)	1,373 (1%)
Currently Smoking (%)		
No	82 (74%)	94,110(72%)
Yes	20 (18%)	24,685 (19%)
Not ascertained	9 (8%)	12,246 (9%)
Sum of weights	215,662	219,364,212

Abbreviations: GED: General Education Dipolma, HS: High School, MSA: Metropolitan statistical areas

Total Expenditures - Approach 1 & Approach 2:

The *'treated prevalence'* refers to 111 *'person-year'* cases, and the '*affected prevalence'* (HNC–specific expenditures) refers to 105 *'person-year'* observations. Therefore, 6 observations reported to have HNC and had medical event(s) that were not related to HNC. The *'average annual'* healthcare expenditure of the analytic sample without HNC was $4,384 (USD 2008). The results of the total expenditure estimation of HNC respondents are given in Table 9.

Table 9: Results of total expenditure estimation of HNC respondents

	Number of observations	Per 'Person-Year' Mean* (SE)	Direct Medical Expenditure National Estimate*
Total Expenditures			
Method 1: Sum All Medical Costs	111	$14,733 (±2,006)	$3.18bn
Method 2: Disease Specific Medical Costs	105	$6,884 (±1,600)	$1.41bn

*US 2008 dollars

It may appear that $14,733 per person is quite low for respondents with HNC but the nature of healthcare utilisation may explain this. Of the 978 medical events, Figure 15 shows that ambulatory care (office-based & outpatient visits) is the most common medical event for respondents with a history of HNC. The mean HNC-specific ambulatory visit expenditure is $395 (95% CI: $329 to $461). It should be noted that inpatient events account for merely 2% of all events but for over 40% of expenditures in this sample. The mean HNC-specific inpatient expenditure is $13,291 (95% CI: $3,212 to $23,369) per respondent with medical expenditure. It is therefore plausible to assume that these HNC respondents may no longer be in receipt of active care for their cancer and that must therefore be borne in mind for the low estimate of average total expenditure. This issue is returned to later in the thesis.

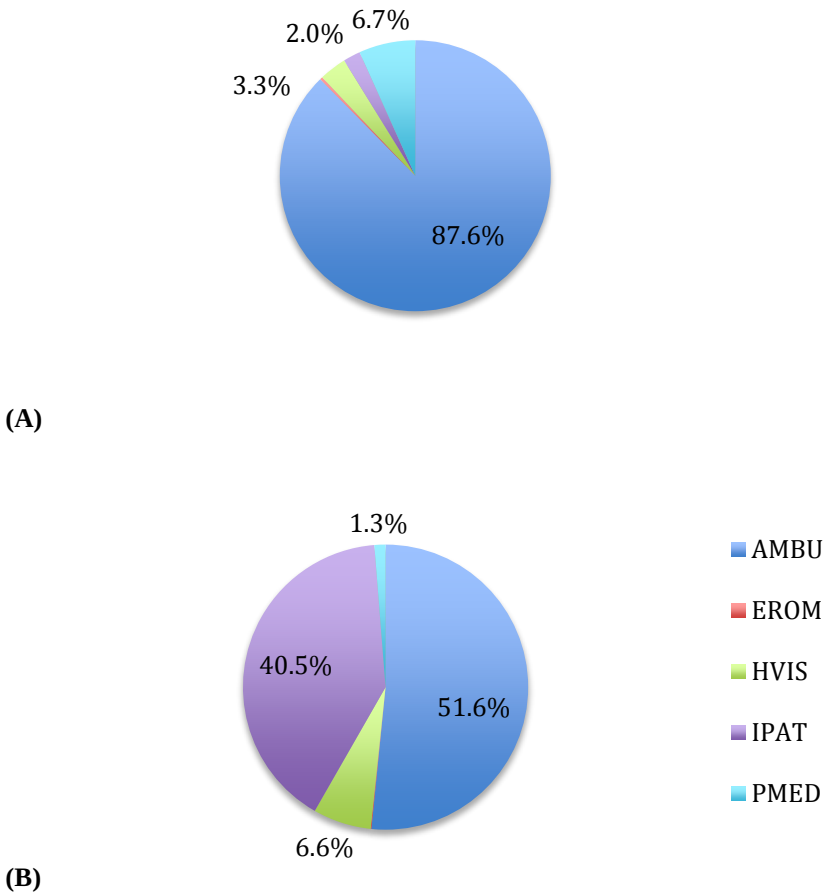

Figure 15: Percentage of disease-specific HNC direct medical expenditure by (A) event type (B) expenditure amount in MEPS (2003-2008)

Code: AMBU – Ambulatory visits (Outpatient and office-based medical provider visits) EROM – Emergency room visits, HVIS –Home health visits, IPAT- Hospital inpatient stay, PMED- Prescription medicine

With MEPS, public policy-makers can also infer the distribution of the economic burden of care and plan accordingly. For HNC-related events, over 40% is paid for by private health insurance and Medicare accounts for 35% of expenditures (Figure 16). It should be possible for government analysts to combine epidemiological and expenditure data to see how much they are potentially liable for.

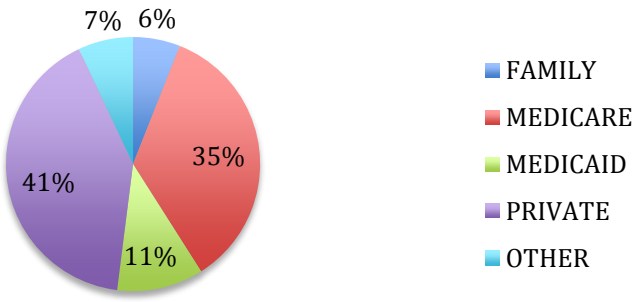

Figure 16: Proportion of disease-specific direct medical expenditure events by payer in MEPS (2003-2008)

Incremental Expenditures: Matching Approach (Approach 3)

Two MEPS studies used respondents with disease-specific expenditures as their analytic sample for estimating incremental expenditures (Balu and Thomas, 2006)(Sullivan et al., 2011) but most MEPS analyses estimate the incremental expenditure based on respondents that have reported the condition of interest. This is a subtle difference that may be important to an accurate estimate of a mild condition where patients don't actual need medical treatment (e.g. short-sightedness or exercise-induced asthma)

For this analysis, the *'treated prevalence'* estimate takes into accounts any medical event and not just HNC-specific expenditures. Table 10 shows that the mean difference in expenditure between the groups attributed to the presence of HNC is $7,251 and multiplying by the survey weights of HNC cases (See Table 8) gives a national estimate of $1.81bn. Seven controls had $0 expenditures and the largest annual expenditure of a control observation was $64,042. In comparison, the HNC cases ranged from $193 to $108,500.

Table 10: Matching of Head and Neck Cancer cases based on MEPS variables

	N	Mean	95% Confidence Interval	Mean Difference in Expenditure
HNC Cases	111	$14,733	$13,557 - $15,909	$7,251
Controls[#]	111	$7,482	$6,551 - $8,413	
National Estimate*				$1.81bn

*US 2008 dollars. Multiple sum of survey weights from cases by mean to generate a national estimate.
#Age, sex, race, insurance status, number of priority medical condition and year of data collection using GMATCH routine.

Incremental Expenditures: Regression Approach (Approach 4)

The reported GLM regression figure (Table 11) is based on a complete case analysis where all cases had positive expenditures. The modified Park test indicated that the expenditure variable followed a Poisson distribution. (Variance is proportional to mean, λ=1 in Eqn.2) However, the log-link function yielded significant p-values for the Pearson correlation test, Pregibon link test and the Hosmer & Lemeshow test. There is no single test that identifies the appropriate link, we would ideally hope that all 3 tests would be consistent in yielding nonsignificant p-values (Glick and Doshi, 2011). The GLM *'counterfactual regression predictions'* method estimated the incremental cost attributable to HNC at $5,069 (95% CI: $4481 to $5658) per person. Extrapolating to the national population by using the pooled weights in MEPS for each respondent with HNC (See Table 8), the *'average annual'* total medical expenditure was calculated to be $1.09bn.

The results of the EEE estimated that the incremental expenditure was estimated to be $2,591 and gave an *'average annual'* (from 2003 to 2008) direct medical expenditure estimate of $754 million. However, the EEE suggested a GLM with a square root transformation and a

Poisson distribution fits the MEPS best (See appendix for Stata output, p.217).

Table 11: Incremental expenditure estimates of Head and Neck Cancer

	Number of observations	Per 'Person-Year' Mean* (SE)	Direct Medical Expenditure National Estimate*
Incremental Expenditures[#]			
Method 4: Regression GLM – Log link & Poisson Distribution	111	$5,069 (±3,614)	$1.09bn
GLM – Extended Estimation Equation	111	$2,591 (±1,142)	$754million

*US 2008 dollars. Used sum of survey weights from cases to generate a national estimate.

Covariates included in regression analysis: Age, gender, race, (ethnicity – dropped in EEE model), education, employment, poverty status, MSA, region, health insurance, self-reported health status, number of priority chronic condition, currently smoking.

Discussion

Four approaches of estimating the direct medical expenditures for a relatively rare (low incidence) condition using the MEPS dataset have been reported in the results section. According to the analyses, the '*average annual*' (from 2003 to 2008), direct medical expenditures for adults with HNC are in the range of $754 million to $3.18bn (in $2008). Compared to the NCI report that HNC has an annual treatment cost of $3.64bn (2010 US$)(NCI, 2012), the MEPS estimates are substantially less. The reason for this is that the NCI estimate is based on an incidence phase-of-care approach and annualised costs were estimated from SEER–Medicare linkage data, which has vastly more observations and includes hospice care (Mariotto et al., 2011). Although there are no gold-standard data sources for estimating the prevalence costs of cancer care, the use of MEPS for national estimates has serious limitations associated with small sample size (Yabroff et al., 2009) From an analyst's perspective, this study highlighted the variation and nuances in direct medical expenditure estimation.

It must be borne in mind at the outset of the discussion that a limitation of this work is the small sample size, which has implications in having great confidence of the results that follow. Approach 1 gives an upper bound estimate using this data source of $3.18bn per year. As this method does not identify the incremental expenditures attributable to HNC, it is not directly comparable to the other approaches - a fact that policy-makers must be aware of and bear in mind if relying on his figure. As shown in the literature review in Chapter 3, the 'total all-cause total healthcare costs' of HNC are likely to be greater than the disease-specific costs. In a MEPS study on Rheumatoid Arthritis, it is a multiple (~x3) of the incremental healthcare expenditures (Fu et al. 2009).

Approach 2 captures only disease-specific events that have been recorded. Also, estimates of cancer-attributable spending based on the

identification of cancer-related encounters are subject to coding errors – e.g. chemotherapy induced nausea. The importance of capturing the specific disease linked events is that it identifies the *'affected prevalence'* and the nature of the disease burden. In HNC, ambulatory care is the most common type of medical event (857/978 ~ 87%) associated with HNC. However, inpatient-care accounts for 40% of expenditures based on 20 events (~2%) and private health insurance (41%) shoulders the majority of the financial burden in HNC. This indicates that MEPS respondents are likely to be long-term HNC survivors. The healthcare utilisation mix of cancer survivors is also important to capture when assessing the burden of a disease and this will be explored further in chapter 5.

For a low incidence condition such as HNC, it is reasonable to assume that practically all expenditures (other than dental) that are directly attributable to the cancer are captured in MEPS given the high response rate to the MPC component. The national estimate was $1.41bn with an 'average annual' per person direct medical expenditure estimate of $6,884 (SE±1,600). This approach does not capture any of the 'spillover' or indirect medical expenditures associated with the disease that an incremental expenditure would capture. For a condition with many secondary effects such as diabetes, epidemiologic formulas based on attributable fractions are needed to give a more accurate estimate of the annual expenditures (Honeycutt et al., 2009). In the case of Asthma, the MEPS disease-specific estimate is 39% of the regression-based estimate of the incremental direct cost of asthma in 2006 (Barnett and Nurmagambetov, 2011).

Approach 3 & 4 attempts to estimate the additional incremental healthcare costs associated with a condition. For this reason, statistical models do not rely on disease-specific or procedural coding, and instead compare expenditures between individuals (Miller et al., 1999). How the approaches do this though are methodologically very different, a fact that may impact on the estimates produced and their

subsequent interpretation. The incremental expenditure approach requires subjective judgment regarding the specification of the model to be used, which may potentially lead to bias in both over- and under-estimating expenditures. The likelihood that selection bias associated with undiagnosed HNC will materially affect results is low. It is unlikely that those with undiagnosed HNC would have healthcare utilisation levels distinct from non-HNC patients as early diagnosis of HNC is often missed owing to the non-specific symptoms or symptoms commonly associated with benign conditions.

The GMATCH matching routine is practical when variables are measured as discrete values. As AHRQ predominately use SAS when discussing MEPS code, the decision to use SAS's GMATCH routine seemed logical. For this analysis, each matching variable received equal weight. While this is acceptable, it is not the only and may not be the optimal approach to analyse this data. The mean difference in expenditures was $7,251, which is substantially higher than the regression approach (This is in part due to the fact that all the sample was included and not just positive expenditures). More sophisticated routines exist in R and Stata that use calliper or kernel density matching with propensity scores.[42] Additional research using the MEPS dataset could compare the various techniques within matching to see what difference they make to the reliability of an expenditure estimate.

Further research could compare other algorithms and test the use of MEPS population survey weights as a matching variable. Researchers at Johns Hopkins School of Public Health (JHSPH), have recently examined the incorporation of survey weights with propensity score matching (Dugoff et al., 2014). They recommend including the survey weight as a predictor in the propensity score model. The survey weight may capture relevant factors, such as where individuals live, their demographic characteristics, and perhaps variables related to their

[42] Using Stata user command - psmatch2 – The Average Treatment Effect on the Treated (ATT) was $4,864 with a bootstrapped standard error (±SE 1,903)

probability of responding to the survey (Dugoff et al., 2014). The other point to make is the difference in the sample versus population average treatment effect can occur and more advancement is likely to occur in this field.

Specifications of regression models are often based on a conceptual framework such as the Andersen model of health services utilisation.[43] Categorical measures of self-reported health status have been shown to be good predictors of subsequent use of medical care and are included in this analysis (van Doorslaer et al., 2000). Indeed, the case for health status as the source of latent heterogeneity in healthcare use is strong (Deb and Trivedi, 2002). As seen in Table 9, there are large differences among those with and without HNC in a number of variables including self-reported health status and the number of 'Quality Priority Conditions' (QPC). Cancer patients typically have more comorbidities than those without (Ogle et al. 2000) (Smith et al. 2008). Therefore, the mean annual expenditure of HNC respondents ($14,733, SE±$2006) is likely to consist of a number of other conditions and not just HNC. In this analysis, a proxy for comorbidity using a count of QPCs was constructed. This method was chosen, as it is the easiest to interpret and most straightforward to implement. Prescribing consistency when adjusting for comorbidity is difficult, as no single comorbidity measurement appears to be the best predictor of healthcare expenditure (Farley et al., 2006). One could argue that some measure is needed and that using the count of QPCs as a proxy for comorbidity can at least be applied across MEPS expenditure studies quite easily.

In the literature review, it was noted that of the GLM regression studies only eight out of fourteen studies made reference to model specification and diagnostic tests. In this analysis, the modified Park test suggested that the GLM use a Poisson distribution. The literature

[43]Andersen's model is associative rather than causal in nature. This model is reconciled with an excepted utility framework in chapter 5.

review showed that only one other study used a Poisson distribution as suggested by model diagnostics (Kamble and Bharmal, 2009). However, the specification tests (Link test, Pearson test, and Hosmer & Lemeshow test) did detect problems with the log-link model, which suggests using a nonstandard link function instead. An estimator that attempts to relax the limitation of pre-specifying a scale of estimation and a functional form of heteroskedasticity is the EEE (Basu et al., 2006)(Basu and Rathouz, 2005). Comparing the regression-based incremental expenditure estimate showed that GLM was $5,069 (SE±$3,614) and EEE was $2,591 (SE$1,142). This demonstrates how big a difference the model can make to the estimate of the per person incremental healthcare expenditure.

The reliability of regression models is dependent on the model used. A MEPS study on hypertension compared six econometric models and based their reported model on goodness-of-fit statistics - root mean square error (RMSE), mean absolute error (MAE) and the scale free Theil's statistic (Basu et al., 2011). The conventional wisdom is that no single model is best for all cases but comprehensive model checking is recommended. With MEPS, future regression based analyses can include a plethora of models (e.g. Finite mixture models if distribution thought to be multimodal) in Stata as code has been made freely available and textbooks become available to compare models in terms of a host of performance parameters such as mean absolution prediction error (MAPE) and the Copas test for overfitting.[44] It is also possible that a *'gold standard'* approach of constructing a matched cohort and then performing a regression analysis could be used for MEPS data. This is probably more suitable for a higher prevalence disease than HNC. This suggestion has recently been implemented for asthma (Rappaport and Bonthapally, 2012). Analysts may feel that a balance must be struck between full disclosure of all possible results

[44] The MAPE is a measure of predictive accuracy. The MAPE summarises how close yhat is to y for each observation (Deb and Burgess, 2003).

and the presentation of the best estimates with explicit justification provided.

Conclusion

This empirical analysis showed that a range of estimates of the direct medical expenditures of HNC could be reported based on four established approaches using MEPS. This analytic approach has the potential to standardise the reporting of direct medical expenditures estimates using MEPS. However, limits on the analyst time may preclude such an approach and policy-makers to absorb such detailed analysis. Reporting an incremental expenditure estimate (matching or regression) is theoretically best and the size of the MEPS dataset does allow for identifying a suitable comparison group. The regression approach is amenable to researcher bias hence the usefulness of explicit justification by way of diagnostic tests.

While it is accepted that policy-makers are not the only audience for such studies, guidance on good practice would be helpful. As stated in chapter 3, many COI studies in the US are not comparable but for studies that use the MEPS, best-practice guidelines could ensure that analysts are not engaging in one-upmanship and that estimates are reliable for policy-makers to use. In the absence of this, the *caveat emptor* will increasingly ring hollow and the value of such studies shall increasingly be called into question.

Chapter 4 - MEPS Literature Review:

References for the 38 healthcare expenditure MEPS studies published from 2005 to January 2013 that was used in the literature review are outlined below. **COM:** Comorbidity was accounted for in the model. **GLM:** Generalized Linear Model was used in the analysis. **LOG:** Logarithm ordinary least squares regression model was used in the analysis. **Tests:** Specification and diagnostic model tests.

Approach 1 only:

Cisternas, M.G. et al., 2009. Trends in medical care expenditures of US adults with arthritis and other rheumatic conditions 1997 to 2005. *The Journal of Rheumatology*, 36(11), 2531–2538. **(COM)**

Liptak, G.S., Stuart, T. & Auinger, P., 2006. Health care utilization and expenditures for children with autism: data from U.S. national samples. *Journal of Autism and Developmental Disorders*, 36(7), 871–879.

Approach 1 & Approach 4:

Simons, W.R., Rosenblatt, L.C. & Trivedi, D.N., 2012. The economic consequences of rheumatoid arthritis: analysis of Medical Expenditure Panel Survey 2004, 2005, and 2006 data. *Journal of Occupational and Environmental Medicine*, 54(1),48–55.

Approach 2 & Approach 4:

Miller, J.D. et al., 2005. Direct costs of COPD in the U.S.: an analysis of Medical Expenditure Panel Survey (MEPS) data. *COPD*, 2(3), 311–8.

Monheit, A.C., Vistnes, J.P. & Rogowski, J.A., 2009. Overweight in adolescents: implications for health expenditures. *Economics and Human Biology*, 7(1), 55–63. **(GLM) (Tests)**

Honeycutt, A.A. et al., 2009. Comparing Cost-of-Illness Estimates from Alternative Approaches: An Application to Diabetes. *Health Services Research*, 44(1), 303–320. **(GLM) (Tests) (COM)**

Martin, B.I. et al., 2008. Expenditures and health status among adults with back and neck problems. *JAMA*, 299(6), 656–664. **(GLM)**

Martin, B.I. et al., 2009. Trends in health care expenditures, utilization, and health status among US adults with spine problems, 1997-2006. *Spine*, 34(19), 2077–2084. **(GLM)**

Olin, G., Machlin, S. & Rhoades, J., 2008. *Estimating the Cost of Illness: The Case of Diabetes*, Agency for Healthcare Research and Quality. Available at: http://gold.ahrq.gov **(LOG) (COM)**

Yelin, E. et al., 2007. Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons with 1997. *Arthritis and rheumatism*, 56(5), 1397–1407. **(COM)**

Approach 3 only:

Farley Short, P., Moran, J.R. & Punekar, R., 2011. Medical expenditures of adult cancer survivors aged <65 years in the United States. *Cancer*, 117(12), 2791–2800. **(COM)**

Lurie, I.Z., Manheim, L.M. & Dunlop, D.D., 2009. Differences in medical care expenditures for adults with depression compared to adults with major chronic conditions. *The Journal of Mental Health Policy and Economics*, 12(2), 87–95. **(COM)**

Yabroff, K.R. et al., 2009. Comparison of approaches for estimating incidence costs of care for colorectal cancer patients. *Medical Care*, 47(7 Suppl 1), S56–63.

Approach 4:

Balu, S. & Thomas, J., 3rd, 2006. Incremental expenditure of treating hypertension in the United States. *American Journal of Hypertension*, 19(8), 810–817. **(LOG) (COM)**

Barnett, S.B.L. & Nurmagambetov, T.A., 2011. Costs of asthma in the United States: 2002-2007. *The Journal of Allergy and Clinical Immunology*, 127(1), 145–152. **(GLM) (Tests) (COM)**

Basu, R. et al., 2011. Lifetime medical expenditures among hypertensive men and women in the United States. *Women's Health Issues,* 21(3), 246–253.

Bhattacharyya, N., 2011a. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. *The Annals of Otology, Rhinology, and Laryngology*, 120(7), 423–427. **(COM)**

Bhattacharyya, N., 2011b. Incremental healthcare utilization and expenditures for allergic rhinitis in the United States. *The Laryngoscope*, 121(9), 1830–1833. **(COM)**

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Papers that use all medical expenditures associated with a disease approach:

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Chapter 5: Healthcare Utilisation of Cancer Survivors – The Irish situation

The initial motivation for this chapter stems from the fact that individuals with HPV-related HNC have better survival rates than traditional HNC patients. A US study estimated that the 2-year survival rate of HPV-related HNC is estimated to be 95% (Fakhry et al., 2008). One of the factors identified in the economic burden literature review (chapter 3) was that the rehabilitation needs of patients with HNC are multiple, varied and prolonged. The functional deficits in HNC survivors arise from not just the cancer but also from organ preservation treatment approaches such as chemoradiation.

These deficits encompass diminished quality of life, weight loss, xerostomia (dry mouth), dysphagia (difficulty in swallowing) and need for gastrostomy (nutritional feeding) tubes (Tippett and Webster, 2012). Encouragingly, research has shown that patients with HPV-related HNCs had fewer swallowing deficits and earlier removal of feeding tubes than traditional HNC (Tippett and Webster, 2012). In contrast, the risks of psychosocial care needs are greater in the HPV-related cohort (Gold, 2012). The emotional distress principally owning to the demographic profile as well as the viral cause of their tumours (Gold, 2012). More generally the adverse effects (also so-called late-effects of treatment) do not cease immediately and the typical cancer patient will probably utilise a variety of healthcare services for a significant period of time after the initial treatment phase. These survivors are identified as the 'affected prevalence' in chapter 4.

Irish data on HNC survivors was unavailable for analysis and therefore a broader cancer survivorship perspective was taken. As in most industrialised countries, the outcomes of people with cancer in Ireland have improved steadily over the last 20 years. The average survival

within five years of diagnosis has gone from 46.7% in 1994-1999 to 61.3% in the 2008-2010 time period (NCRI, 2013) – See Figure 17. [45]

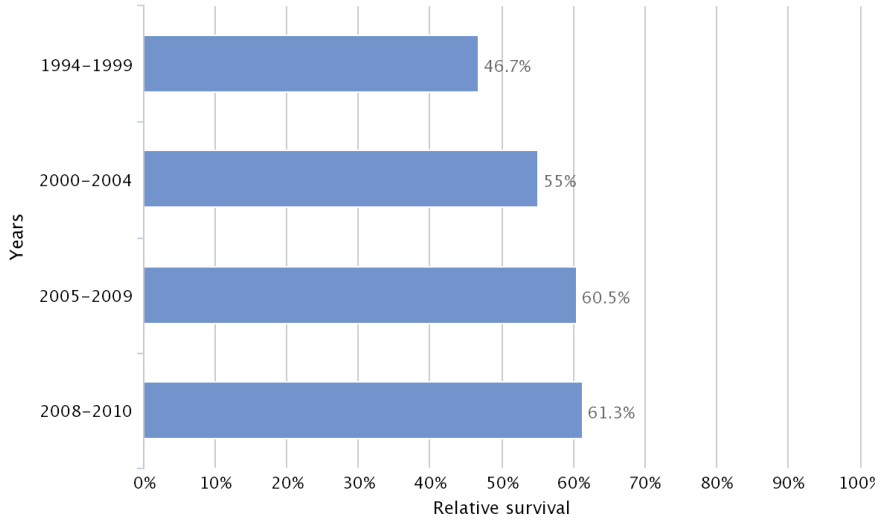

Figure 17: 5-year survival trend of all cancers in Ireland from 1994 to 2010 (NCRI 2014)

According to the NCRI, a total of 104,300 cancer patients were diagnosed since January 1994 and were still alive at the end of 2010 (NCRI, 2013). As the number of survivors increases, so will the demand for cancer-related healthcare services. How best to manage this extra demand is likely to present a growing issue for Irish cancer policy-makers, especially given the increasingly constrained resource environment within which it now operates. It is within this context that an examination of the relationship between cancer diagnosis and the service use, as well as how the level of service use post diagnosis warrants investigation.

Aim and Objectives

The aim of this chapter is to examine the level of health service utilisation association with a cancer diagnosis and to investigate how that level changed as the time since cancer diagnosis increased. This should assist policy-makers to plan for a circumstance in which there

[45] When stratified by gender, survival in men went from 42% in 1994-1999 to 60% in 2005-2009 and from 52% to 62% over the same period in women (NCRI, 2013).

are an increasing numbers of cancer survivors. The specific objectives were to estimate the incremental service use controlling for a range of covariates associated with a diagnosis of cancer; to examine the impact on the level of service use associated with the interval since diagnosis; to compare count and bivariate probit models in terms of the relationship between service use, and time since cancer diagnosis.

5.1 Introduction to Cancer Survivorship and Healthcare Utilisation Research

The concept, labelling and semantics of cancer survivorship has been debated in the literature ((Twombly, 2004)(Bell and Ristovski-Slijepcevic, 2013)(Tralongo et al., 2013). In the US, the Institute of Medicine (IOM) and the NCI's Office of Cancer Survivorship emphasize the distinction between the actual cancer survivor and the cancer survivorship phase, referring to a distinct phase in the cancer trajectory between primary treatment, cancer recurrence and end of life (IOM, 2005)(Rowland et al., 2006). This distinction is important when considering the health, well-being and healthcare utilisation of individuals with a history of cancer and goes beyond the biomedical cut-off point of five years, an often used metric of survivorship (Dockser-Marcus, 2013).

In 2008, IARC's GLOBOCAN project, that estimates the incidence, mortality and prevalence of cancer, considered those alive after 5-years to be 'cured'. IARC acknowledged that this is often not the case especially in breast cancer (IARC, 2008) and cancers such as multiple myeloma where patients can live longer with the disease without being cured (Kumar et al., 2013). A lot of men with a diagnosis of prostate cancer undergo 'active surveillance' as their cancer is slow growing and judged not to be terminal. As knowledge of the causal agents of cancer have evolved, so too has the group of cancers viewed as survivable [e.g. HPV-related HNC] (O'Rorke et al., 2012) and with it the challenge to policy-makers in planning healthcare services.

Healthcare Utilisation of Survivors

An international review of the literature focusing on the patterns and determinants of health service utilisation of cancer survivors divided their analysis into four categories: primary healthcare, follow-up care surveillance, preventive care and hospital care including mental health

services (Treanor and Donnelly, 2012). The authors conclude that use of a specific type of service rather than adopting a 'whole-system' approach is a shortcoming of most studies that they reviewed and recommend that future research should address this shortcoming (Treanor and Donnelly, 2012).

The authors advocated the Andersen Behavioural Model (Figure 18) as an appropriate framework for studying and understanding health service use of all individuals including cancer survivors.[46] Models of healthcare utilisation provide guidance for defining variables, specifying the relationships between them, and evaluating programs and policies concerned with access to and utilisation of healthcare services. Andersen's behavioural model describes healthcare utilisation in terms of predisposing (e.g. Age, gender, marital status), enabling (e.g. Education, place of residency and health insurance) and need (e.g. Presence of disease such as cancer, self-assessed health) factors (Andersen, 1995). The model is not explicitly grounded in an economic model of decision-making. That said, it can, however, be readily related to models such as that of expected utility – predisposing, enabling and need factors providing examples of cost, benefit or how these might be related to each other in terms of time preference or risk aversion. Given the myriad of factors that can impact on access and service use including, financial and non-financial costs, financial and non-financial benefits, risk aversion, time preference, access to and ability to process information as well as the role of clinicians (and potentially spouses) in decision making it was decided not to develop an explicit model, while using the Andersen framework for ease of exposition.

[46] A review identified four major types of utilisation models: (a) models of patient decision making, grounded in sociological theory and research; (b) the health belief model, based in psychological theory; (c) economic models of the demand for medical care; and (d) the behavioural model of health services utilisation that has guided much health services research on access to and utilization of healthcare services (Aday and Andersen, 2005). Another pertinent economic theory of healthcare utilisation is related to the principal agent framework (Schneider and Mathios, 2006).

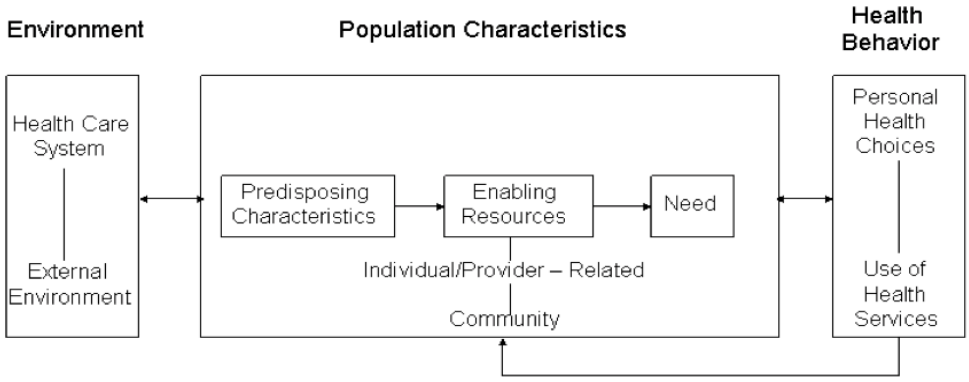

Figure 18: Andersen model of healthcare utilisation (adapted from Andersen 1995)

Literature Review on Cancer Survivors' Healthcare Utilisation

This emerging field of survivorship research is particularly strong in the US, UK and the Netherlands. Studies have examined issues stratifying by the type of services analysed (e.g. hospital, physician or drugs), the purpose of care (e.g. primary or secondary) and the unit of analysis (e.g. contact, volume or episode-of-care). The most common sentiment across all studies is that this burgeoning cohort over the next 10 years presents a significant challenge to the healthcare system (de Moor et al., 2013). An issue of relevance to the examination pursued here is the relationship between time since diagnosis and cancer type with healthcare use.

A Norwegian study assessed cancer survivors (Testicular, colorectal, prostate, breast, gynaecological and lymphoma/leukaemia) use of GP services, specialist physician in a hospital setting, physical therapy and complementary and alternative medicine (Nord et al., 2005).[47] The authors concluded that cancer survivors used healthcare services {Odds Ratio (OR) = 1.96 (95% CI 1.66 to 2.31, p-value <0.001)} and received social welfare benefits {OR = 1.39 (95% CI 1.10 to 1.76, p-value <0.001)} more often than the controls (Nord et al., 2005). In

[47] In Norway, every individual has a unique 11-digit personal identification number given at birth and this allows for cross-referencing to health registries.

Denmark, long-term breast cancer survivors (5-15 years post diagnosis) reported statistically significant more healthcare utilisation of specialist visits, outpatients' appointments, physiotherapy and chiropractor (61% versus. 56%; age-standardised risk ratio (SRR): 1.10; 95% confidence interval (CI) 1.05–1.15), than women of the general population (Peuckmann et al., 2009).

A 2007 Dutch study compared only GP and specialist visits of long-term survivors of endometrial cancer, prostate cancer and non-Hodgkin's lymphoma (Mols et al., 2007). Both younger (<70 years) and older (>70 years) cancer survivors visited their medical specialist (71-94% vs. 48-63%), but not their GP (82-95% vs. 78-89%), significantly more often compared to the age-matched general Dutch population (Mols et al., 2007). By 2012, primary healthcare use was significantly increased 2 to 5 years after diagnosis of cancer especially in younger patients without a chronic disease (Heins et al., 2012). The mean annual number of primary care contacts increased compared with control patients by 24% (3.94 vs. 3.56 visits) in patients with breast cancer ($P < 0.001$) and by 33% (4.37 vs. 3.72) in patients with prostate cancer ($P < 0.001$). These changes may be due the emergence of national practice guidelines - The Dutch Ministry's health council reports on survivorship emanate from 2007 and culminated in the introduction of National guidelines in the Netherlands at the end of 2010.[48]

Notable US studies looked at utilisation of mental health services (Hewitt and Rowland, 2002) and commented that cancer survivors reported significantly greater contact in the past year with a mental health provider than the general population (7.2% vs. 5.7%). Stratifying by cancer type, from 1997 to 2001 colorectal cancer

[48] http://www.oncoline.nl/index.php?language=en(accessed 24th April 2014) - A presentation entitled: "Cancer survivorship plan in the Netherlands: a guideline for professionals in oncology by S. Kerstenon behalf of the Guideline working group Cancer survivorship care Comprehensive Cancer Centres identified Ministry's health council report http://www.g-i-n.net/document-store/g-i-n-conferences/chicago-2010/presentations-chicago-2010/kersten-s65.pdf

survivors' primary care physician (PCP) visits increased from a mean of 4.2 to 4.7 (p-value <0.001) while oncology visits decreased from 1.3 to 0.5 (p-value <0.001) (Snyder et al., 2008). For breast cancer survivors from 1998 to 2002, PCP visits increased slightly from 4.2 to 4.3 visits and oncology specialist increased from 2.2 to 2.5 visits (adjusted *P* trend over time <0.001). For both colorectal and breast cancer survivors who visited both a PCP and oncology specialist, they were more likely (p<0.05) to have received recommended preventive care (Snyder et al., 2008)(Snyder et al., 2009).[49] These studies noted that clarifying the roles of PCPs and oncology specialists during follow-up could improve the quality of care for survivors.

In the UK, studies utilising the General Practice Research Database have looked at primary care consultation, receipt of cancer screening and preventive care (Khan et al., 2011)(Khan et al., 2010). Breast and colorectal cancer survivors had one more consultation per year with their GP compared with controls up to five years after diagnosis; rates then converged at 10 years post-diagnosis. Prostate cancer survivors consistently consulted up to three more times with their GP than controls. These increases in consultation rates are leading to an impact on service capacity (Khan et al., 2011). Using Hospital Episode Statistics (HES), Maddens et al. (2011) state that a considerable proportion of cancer survivors in the UK have a high level of hospital utilisation soon after diagnosis or before death, but the large majority of them are neither recently diagnosed nor near the end of their life, and do not utilise acute health services for cancer-related care.

Limitations of a lot of the aforementioned studies include the cross-sectional design, which does not allow interpretation in terms of causation; utilisation is self-reported and studies that are survey based have a high degree of non-respondents. Perhaps, the biggest limitation

[49] Survivors who saw both PCPs and oncologists were most likely to receive influenza vaccination, mammograms, and cervical cancer screening (p <0.05); survivors who saw PCPs only were most likely to receive cholesterol screening and bone densitometry (p<0.05)

in some retrospective database analyses is that it is not possible to confirm the reasons for the consultation. In the MEPS analysis, condition-event link files exist that allow disease-specific utilisation and expenditures to be captured. This level of detail is not always available to an analyst.

A pertinent point to make is that an appreciation of the structure, funding and entitlement nature of the healthcare system is pivotal in any analysis of cancer survivor's healthcare utilisation. The recent literature review by Treanor and Donnelly (2012) state that: *"There is a need to give consideration to the merits of conducting comparative healthcare system research, particularly given the differing role of the oncologist between healthcare systems and the role of insurance in obtaining access to care in USA studies"*.

Therefore, if healthcare systems differ in terms of the financial barriers to access or in terms of the relationships between primary and hospital sectors, different patterns might well be expected to exist between systems grounded, within the Andersen framework for example in issues of enabling factors. It is important therefore to have some understanding of how the Irish healthcare system operates and how this differs from other systems one might like to compare levels or patterns of use with.

Irish Healthcare System

The Republic of Ireland has a mixed publicly-privately funded healthcare system. About four fifths of total health expenditure was publicly funded in 2007 (Brick et al., 2010). Private health insurance and out-of-pocket payments accounted for the remainder. The public/private interaction in the Irish healthcare system means that private funded services can be delivered in acute public hospitals. Consultant specialists in acute public hospitals – depending on their employment contract – are permitted to treat private patients up to a

maximum of 20-30 per cent of their complexity-adjusted workload (Brick et al., 2010).

There are three main categories of entitlement to access healthcare services in Ireland (See Table 12)(O'Reilly et al., 2011). Eligibility for a medical card is largely determined on the basis of income (McDaid et al., 2009). Entitlement to medical card, at the time of the TILDA study, was means-tested in those under 70; from 2001 to 2008 was universal in those aged 70 and older but changed to means-testing in 2009. GP visit cards are also allocated on the basis of income, with income thresholds being 50 per cent higher than that for medical card holders (Brick et al., 2010).[50] In 2009, medical card holders and GP visit card holders comprised of 33.2 per cent and 2.2 per cent of the population, respectively (Department of Health, 2010). All citizens are entitled to acute treatment in public hospitals. Those without a medical card must pay a contribution for visiting primary care physicians (range €40-65) and for hospital attendance – emergency and outpatient (€100 unless referred by GP), inpatient or daycase has a daily hospital charge of €75 as well as the full costs of prescription medications (Brick et al., 2010). In 2009, approximately 46% of the population had private health insurance (HIA, 2009). In Ireland, private health insurance provides mostly supplementary cover (e.g. faster access to specialists & treatment in private hospitals) (Harmon and Nolan, 2001). A further 5% held both a medical card and private health insurance (Brick et al., 2010).

[50] GP visit cards were introduced in October 2005 (Nolan and Smith, 2012).

Table 12: Health care charges for public and private patients (O'Reilly 2011)

	Public patient		Private patient
	Medical card holder	Non-medical card holder (including GP visit card holder	
GP visits	Nil	Charge determined by GP	Charge determined by GP
Prescription medicines	50c per prescription item up to maximum of €10 per family per month	Free above €120 out-of-pocket payment per month No charge for certain long-term illnesses/conditions	
Public hospitals			
• Emergency Room	Nil	€100 unless referral by GP or subsequently admitted to hospital	
• Outpatient department	Nil	€100 unless referral by GP or subsequently admitted to hospital	
• Daycase/ Inpatient	Nil	Daily hospital charge of €75 (up to a maximum of €750 in any 12 consecutive months	Daily hospital charge as per public patients plus a hospital maintenance charge and consultant fees [a]

[a] The hospital maintenance charge is a per diem charge, which varies according to the type of treatment (inpatient or daycase), accommodation (private or semi-private bed) and hospital. In 2011, this charges ranges from €193 for daycase in district hospitals to €1017 for private accommodation in certain hospitals, such as regional hospitals.

Previous work has noted a significant role for non-need factors in primary care use in Ireland (Nolan and Nolan, 2008). A panel study by Nolan (2007) suggested that the only significant non-need factors are medical card eligibility and employment status (Nolan, 2007). Similarly, the study by Nolan and Nolan (2008) indicated that medical card patients have a significantly higher probability of visiting their GP and also a higher number of visits than those that are private patients. Whether this all means that medical card patients visit too frequently or private patients too infrequently, or indeed both, is impossible to say, as a clear notion of the optimal number of visits is not known.

Using a difference-in-difference approach, Madden et al. (2005) noted that there was no evidence of supplier-induced demand by GPs for private patients over medical card patients. Back in 2001, the role of private health insurance was seen in the increased probability (3%) of having inpatient care compared to those without any coverage (Harmon and Nolan, 2001).

Research on healthcare utilisation using the TILDA dataset also highlights the differential utilisation rates between medical cardholders and non-medical cardholders (McNamara et al., 2013). This also indicates that the price faced by users is a strong determinant of healthcare utilisation in Ireland and is supported by recent analyses of GP visit cards that suggested that 'pent-up demand' was an explanation for the absence of a significant difference in GP visits between full medical cardholders and GP visit cardholders (Nolan and Smith, 2012).[51] The other non-need factor that is relevant to Ireland is regards residency - rural areas having the lowest access to GP services with many elderly people residing there (Morrissey et al., 2008).

Unobserved Heterogeneity

A likely issue to arise with any analysis of healthcare utilisation using survey data is how best to account for unobserved heterogeneity. This issue can arise from either the demand-side or the supply-side. The unobserved individual demand-side heterogeneity can relate to characteristics such as ability (health literacy will be discussed in chapter 6) or motivation, genetic inheritance, attitudes towards medical care or time preference rates (Nolan, 2007). A particular aspect of unobserved heterogeneity is that related to risk aversion – what some have referred to as the 'worried well'. This might impact on not only the likelihood of using services but also the patterns of services used. Some, including cancer survivors, may for example, be

[51] The fact that a GP visit card recipient now has a similar level of utilisation, as someone with a full medical card is suggestive of 'pent-up demand'.

more likely not only to use GP services relative to others but also to press for referral onto a specialist. A common issue in long-term cancer survivors is anxiety of recurrence either as second primary malignancies or new cancers (Mitchell et al., 2013). Unobserved supply-side heterogeneity can similarly exist related to the role of the clinician as agent of the patient. For example, in patients with a particular diagnosis – including cancer – it could be that once diagnosed, the patient is forever more under the agency, of the treating oncologist. It could also be that the GP feels ill equipped or educated to care for patients with cancer. Equally it is conceivable that GPs exhibit different degrees of risk aversion when confronted with different conditions being more likely to refer on such patients to secondary care. Unobserved heterogeneity is thus likely to exist and its source varies. It is important nevertheless in whatever modelling approach is adopted that where this is thought to be material its effects can be accommodated.

Survivorship Healthcare Utilisation Research in Ireland

While various international studies have examined aspects of the need for, and use of, a range of healthcare and social services consequent upon a cancer diagnosis, only recently has long-term health, well-being and healthcare utilisation following cancer treatment been a focus of research in Ireland. Naidoo et al. (2013) interviewed breast cancer survivors discharged to GP care to ascertain their needs in terms of physical, psychological and social factors. For a robust empirical analysis of cancer survivorship, a comparator group is required, which is the biggest limitation with NCRI data. TILDA is the only nationally representative dataset that allows for detailed analyses of health, well-being and healthcare utilisation of cancer survivors compared to people without a history of cancer. [52]

[52] An alternative nationally representative survey may have been the 2007 Survey of Lifestyle, Attitudes and Nutrition (SLAN) but only 1% of that sample had cancer.

5.2 Healthcare Utilisation of Cancer Survivors in Ireland

Data and Methods

TILDA is a two-stage clustered survey of the population aged 50 and older in the Republic of Ireland. A random sample of 640 clusters of 500 to 1,180 residential addresses (community dwelling) was selected according to socioeconomic group (three categories) and geography. Clusters were selected with probability proportionate to the proportion of the population in each cluster aged 50 and older. Forty addresses in each cluster were randomly selected, and all persons aged 50 and older were asked to participate in the study (Layte et al., 2013). During fieldwork, 8,504 interviews were conducted with individuals in 6,279 households, with a response rate of 62%. Interviews were conducted in respondents' homes by way of a CAPI.[53] TILDA is a comprehensive survey with twenty-four distinct sections that cover a wide arrange of topics from demographics, physical and cognitive health, behavioural health, employment, social connectedness and sources of income (Kenny and Nolan, 2014).

The specific aims of TILDA set out by the team at Trinity College Dublin is to: *"Provide comprehensive, internationally comparable baseline data on older people in Ireland, leading to improvements in policy and planning"* (Kenny and Nolan, 2014). In common with other longitudinal studies of ageing, TILDA is a multidisciplinary study with three principal domains: Health, economics and social circumstances (Kenny and Nolan, 2014). Although the TILDA sample is representative of community dwelling adults aged over 50 in Ireland, it is not, as yet, fully representative of those who have moved to an institutional setting. TILDA initially recruited only those who were community dwelling.

[53] More detail on the sampling methodology and data collection used in TILDA can be found in Whelan and Savva (2013). http://tilda.tcd.ie/publications/ List of publications that cover a while range of social gerontology (Last accessed: 22nd April 2014).

Description of Variables - Dependent Variable

The healthcare utilisation section of TILDA consists of thirty-seven questions entirely about the respondents' interaction with the healthcare system. Relevant questions were framed as: *'In the last 12 months how often did you visit…'* a particular healthcare service? In this analysis, the focus is on the services that cancer survivors are likely to use - GP visits; outpatient hospital visits (separating out day-case procedures from office visits) overnight hospital admission and emergency room visits. These variables are counts. A healthcare service variable was also constructed based on use of allied healthcare services provided by the State. The question was framed: *'In the last 12 months, did you receive any of the following State services*?' The list of State services is given in Table 2. As each of these variables was coded: 1- Yes and 0 – No, this variable called (public services) is also converted into a count variable (See Table 13 for more details).

Table 13: TILDA variables and description

Variable	Description
Dependent Variable	
GP Visits	In the last 12 months about how often did you visit the GP?
Outpatient	In the last 12 months about how many visits did you make to a hospital as an outpatient?
Daycase	In the last 12 months on how many the outpatient visits did you have a substantial procedure, operation, or test? Sometimes called day-case procedures
Inpatient admission	In the last 12 months on how many occasions were you admitted to hospital overnight?
Emergency room	In the last 12 months on how many times did you visit a hospital emergency department (sometimes called A&E or Accident and Emergency) as a patient?
Public services	In the last 12 months did you receive the services of a public nurse? Occupational therapy services? Dietician services? Home help services? Physiotherapy services? Chiropody services? Care attendant? Daycare services? Dentist? Speech and language therapy services? Psychologist? Meals-

	on-wheels? Optician? Hearing aid services? Respite care services? This variable was constructed as a count variable.
Main Independent Variable	
Cancer 0/1	1=Time since diagnosis 0 or 1 year (where active treatment is likely to be ongoing), 0 otherwise
Cancer 2/5	1=Time since diagnosis 2 to 5 years, 0 otherwise
Cancer 6/10	1=Time since diagnosis 6 to 10 years, 0 otherwise
Cancer 11+	1=Time since diagnosis 11 years plus, 0 otherwise
Breast Cancer	1=Breast cancer, 0 otherwise
Prostate Cancer	1=Prostate cancer, 0 otherwise
Colorectal Cancer	1=Colon or rectal cancer, 0 otherwise
Other cancer	1=Malignant melanoma (skin), non-Hodgkin lymphoma and cancers from 22 other organs listed in TILDA, 0 otherwise
Explanatory variables	
Age 50-54	1=aged between 50-54 years, 0 otherwise (Comparison group in analysis)
Age 55-59	1=aged between 55-59 years, 0 otherwise
Age 60-69	1=aged between 60-69 years, 0 otherwise
Age 70-79	1=aged between 70-79 years, 0 otherwise
Age 80+	1=aged between 80+ years, 0 otherwise
Female	1=Female, 0 = male
Employed	1=Employed, 0 otherwise
Retired	1=Retired, 0 otherwise
Unemployed/ student/ homemaker	1=Unemployed/student/homemaker, 0 otherwise
Married/LWP	1=Married or Living with partner 0 = Not currently married, single, separated, divorced or widowed
Primary Education	1=Primary education or less, 0 = Secondary education or more
Dublin	1=Lives in Dublin, 0 otherwise
Town	1=Lives in regional city or town, 0 otherwise
Rural	1=Lives in rural location, 0 otherwise
Medical card only	1=Medical card only, 0 otherwise
Health Insurance (HI) only	1=Health insurance only, 0 otherwise
Dual cover	1=Medical card & health insurance, 0 otherwise
No Cover	1=Neither medical card nor HI, 0 otherwise

Number of comorbid conditions (Chronic_1, chronic_2 or chronic_3+)	Count of number of chronic conditions based on hypertension, angina, heart-attack, heart failure, stroke, ministroke, high cholesterol, heart murmur, abnormal heart rhythm, heart trouble, lung, asthma, arthritis, osteoporosis, Parkinson's disease, depression, alcohol dependence, Alzheimer's disease, dementia, memory impairment, ulcers, varicose veins, liver disease and diabetes.
Self assessed health (SAH) status	1=Excellent/very good/good 0 = Fair/poor
Self assessed mental health (SAMH) status	1=Excellent/very good/good 0 = Fair/poor
Activities of daily living (ADL)	1=Has at least one limitation 0 = Has no limitation
Instrumental activities of daily living (IADL)	1=Has at least one limitation 0 = Has no limitation

Main Independent Variable

A respondent with a history of cancer was identified with an affirmative response to the CAPI survey question *"Has a doctor ever told you that you have any of the following conditions?*" The list of conditions included cancer. Respondents with a history of cancer were then asked about the type of cancer (e.g. breast, prostate, colon) and the age at which they were diagnosed. In the publically available TILDA dataset, age of cancer diagnosis was a categorically variable. A special request was made to TILDA in order to get a dataset with this variable in its original format as a continuous variable. Time since cancer diagnosis was calculated by subtracting age at diagnosis from age at time of survey. Cancer survivors were categorised by time since diagnosis as 0 or 1-year (where active treatment is likely to be ongoing); 2-5 years, 6-10 years, and 11 or more years; the latter groupings were informed by a similar US analysis (Yabroff et al., 2004). Given the construction of this variable from the survey questions, it was likely that those respondents that reported a two-year gap

between their age and the age of diagnosis as either undergoing treatment or have just completed treatment (The analysis based on MEPS data on HNC would suggest this). After 2-years, it is plausible to assume that the respondent has finished treatment and is in the early stages of remission or living with the cancer. After 5-years, it likely that the respondent is either in full remission or living with the cancer and after 11 years, it is plausible to think of the cancer diagnosis as a distant event for the respondent.

Explanatory Variables

Explanatory variables were arranged in line with the Andersen Model of Healthcare Utilisation (Figure 18), which was also used by TILDA researchers - McNamara et al. (2013). It is though accepted that these categorizations are not definitive – it could for example be that health insurance is an enabling and/or a predisposing characteristic just as within an expected utility model it might capture differential access to care as well as different tastes and preference for care (McGregor et al., 2008).

The predisposing characteristics are: Gender, age, employment, and marital status. The enabling characteristics are: Education and location. The entitlements were elaborated to include four mutually exclusive groups: Medical card only, private health insurance only, neither medical card nor private health insurance and dual-cover (medical card and private health insurance).[54] The need characteristics are: Number of comorbid conditions[55] - A count variable for the number of chronic conditions captured in the survey, self-assessed health, self-

[54] Medical card variable included GP visit card (n=167 or 1.67% of sample). Both medical card and health insurance variable could also be presented as health insurance (yes/no) or medical card (yes/no).

[55] In deciding to use a simple count of comorbid conditions, the implication is that the assumption is that each condition has equal weight in determining healthcare utilisation. This is a judgement call made, as within TILDA there is no information on the severity of the conditions. While some conditions may seem more serious than others, the information is not there to support this. The other reason is that dummy variables for each condition would use up too many degrees of freedom incorporating separate dummies for each.

assessed mental health, activities of daily living, instrumental activities of daily living.

Methods

Descriptive Statistics

The characteristics of TILDA respondents (over-50 years) with and without a history of cancer are compared. The cancer variable is then stratified by type and time since cancer diagnosis. The descriptive statistics (mean, standard deviation, variance, minimum and maximum) of healthcare utilisation by service is then examined. Histograms are constructed to illustrate the distribution of the number of visits per healthcare service. A final table of the percentage of respondents with a history of cancer by type and time since diagnosis of at least one reported healthcare usage per service is given to clearly demonstrate the difference in healthcare usage compared to non-cancer respondents.

Statistical Analyses - Count Models to Analyse Health Care Utilisation[56]

The basic count data regression model is the Poisson. This model has been shown to be too restrictive (implies equality of the conditional mean and conditional variance) for modelling healthcare utilisation and it neglects unobserved heterogeneity akin to omitted variables. Other models - negative binomial, zero-inflated[57], hurdle[58] or finite-

[56] Many empirical analyses of healthcare services utilisation, use as dependent variable a count variable (non-negative integer valued count y= 0,1, 2…). Several special features of count regression models are intimately connected to discreteness and nonlinearity - a large proportion of zero observations, as well as long right tail of individuals who are heavy-users.

[57] These models allow for the possibility that the zeros are generated by a different process than the positives. An important aim of these models is to solve the problem of excess zeros, i.e. the occurrences of even more zeros than predicted by the negative binomial model. This is known as a zero-inflated negative binomial (ZINB) model

[58]The hurdle model or two-part model for count data was proposed by Mullahy (1986).

mixture models[59] (A particular subclass of latent class models) have been preferred to Poisson in the literature (Jones et al. 2013) and will be discussed next:

1. Negative Binomial (NB)

The unobserved heterogeneity (e.g. anxiety), which generates additional variability in the *y* variable, can be accounted for by introducing multiplicative randomness. This can be modelled as a continuous mixture of the Poisson distribution[60], by specifying the mean as $E[y_i \mid x_i] = \lambda_i$ a deterministic function of the covariates and η_i a random term, which distribution should be defined. The NB model results from assuming that η_i follows a gamma distribution[61] with variance α[62] (see Cameron and Trivedi 1998, 2005 for full derivation). It is the random term, η_i that accounts for the unobserved heterogeneity and the nature and implications of the distribution upon results is what econometricians have debated upon (Greene, 2008). For utilisation of healthcare services by cancer survivors, NB models are unable to account for the unobserved heterogeneity discussed earlier in this chapter. Also, there is evidence that NB models have poor fit in count models with excess zeros and long-tailed distributions and other models may be preferred.

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[59] Finite mixture or latent class models provide a semi-parametric approach for dealing with unobserved heterogeneity

[60] A useful way to motivate the Negative Binomial model is through the introduction of latent heterogeneity in the conditional mean of the Poisson model (Greene, 2008).

[61] The assumption of gamma heterogeneity underlying the mixture interpretation of the negative binomial model is very convenient, but there are other alternatives like lognormal (Greene, 2007) or Poisson (Greene, 2008). The negative binomial model is an example of a continuous mixture model, because the heterogeneity variable, or mixing random variable, *ν*, was assumed to have a continuous distribution (gamma).

[62] The conditional moments are: $E[y_i \mid x_i] = \lambda_i$ and $\nu \sim \text{Gamma}(1, \alpha)$, α is the variance parameter of the gamma distribution, the marginal distribution of *y* in a Poisson-gamma mixture with a closed form. Alternatively, $V[y_i \mid x_i] = \lambda_i + \alpha \lambda_i^{2-k}$ where α is the overdispersion parameter; $\alpha=0$ reverts to the Poisson. Most empirical applications of the NB model consider k=1 (NB1) or k=0 (NB2). In NB1, the variance is proportional to the mean $(1+\alpha)\lambda$. In the NB2, the variance is a quadratic of the mean $\lambda + \alpha \lambda^2$. By default, Stata estimates the NB2 model.

2. Hurdle Models

The hurdle model, or two-part model, relaxes the assumption that the zeros and the positives come from the same data-generating process. The zeros are determined by the density $f_1(.)$, so that Pr [y=0] = f_1(0). The positive counts come from the truncated density $f_2(y|y> 0)$ = $f_2(y)$/ 1 - f_2(0)), which is multiplied by Pr [y> 0] = 1 - f_1(0) to ensure that probabilities sum to unity. Then

$$g(y) = f_1(0) \quad \text{if } y=0$$

$$= f_2(y)\,(1 - f_1(0)) \quad \text{if } y>0.$$

This reduces to the standard model only if f_1 (.) = f_2 (.). Thus, in the modified model, the two processes generating the zeros and the positives are not constrained to be the same. Additional flexibility results from being able to choose suitable component densities. For example, a NB density for the positive counts that accounts for overdispersion (Deb and Trivedi, 2006).

The hurdle model can be interpreted utilising economy theory as a principal-agent type model, where the physician (the agent) determines utilisation on behalf of the patient (the principal) once initial contact is made. Thus, it is assumed that the decisions to seek care are taken by the individual, while the level of care depends also on supply factors. For individuals with a history of cancer, it is plausible that the agent is a hospital specialist early (<2 years) or very late in the survivorship phase (close to death) similar to Maddems et al. (2011) experience in England. It is plausible that at a time since diagnosis >2 years that the agent responsible for care is the GP similar to what happens in the Netherlands (Heins et al., 2012). Hence, this analysis has practical significance to clinical practice in Ireland. The GP is often seen as having a gatekeeping role in the initial access to hospital care including cancer services but less is known about the level of their

involvement in the survivorship phase.[63] Pohlmeier and Ulrich (1995) argue that it is necessary to account for this unobserved heterogeneity, since *"supply side effects are rarely well captured in household data at the micro level"*. Unfortunately, in this analysis, supply-side factors like the number of GPs per capita are not included in the model. The fundamental parts of the two-part model is whether the individual enters the healthcare system or not and once in the system, how much services should they use. In Stata, the hurdle logit-NB2 model can be estimated using the hnblogit user-written command (Hilbe, 2005).

3. **Finite Mixture Model**

Deb and Trivedi (1997) proposed an alternative to hurdle models in empirically modelling of healthcare utilisation. In 2002, they point out that a more tenable distinction for typical cross-sectional data may be between an 'infrequent user' and a 'frequent user' of medical care, the difference being determined by health status, attitudes to health risk, and choice of lifestyle. In the finite mixture model (FMM) (Also called latent class model) formulation of unobserved heterogeneity, the latent classes are assumed to be based on the person's long-term health status, though captured by proxy variables such as self-assessed health status and chronic health conditions may not be sufficient (Cameron and Trivedi, 1998). The two-point finite mixture model suggests the dichotomy between the 'healthy' and the 'ill' groups, whose demands for healthcare are characteristed respectively by low mean and low variance and high mean and high variance.[64] Jimenez-Martin et al. (2002) highlight that the hurdle model is a natural extension of an economic model (principal-agent model), but that the disadvantage of the finite mixture model is that statistical reasoning drives it. A

[63] There are no cancer survivorship guidelines in Ireland.

[64] Teresa Bago d'Uva has also proposed a latent class (LC) hurdle model, which allows for a two-part decision process within each class, as well as intercept and slope heterogeneity in both parts, extending it further to allow the probabilities of class membership to depend on time invariant individual characteristics(Bago d'Uva, 2006).

limitation with this approach is that it does not account for the relationship between different levels of service that an individual with or without a history of cancer would experience in any healthcare system. In Stata, the fmm user-written accommodates other latent class (LC) count data models, the LC Poisson and the LC NB2 (Deb 2007), (Deb, 2012).

Model Selection

Choosing the 'best' count model involves trade-offs between fit, parsimony, and ease of interpretation (Cameron and Trivedi, 2005). The user-written countfit command by Long and Freese (2006) facilitates the task of multiple model comparisons for the four candidate models: Poisson, NB, ZIP and ZINB. The output provides the penalized log-likelihood-based statistics (Vuong)[65] and Akaike and Bayesian information criteria (AIC and BIC respectively).[66] Balancing sensitivity (having enough parameters to adequately model the relationship among variables in the population) with specificity (not overfitting[67] a model or suggesting nonexistent relationships). The

[65] It is possible to test one non-nested likelihood-based model against another, using the likelihood ratio (LR) of Vuong's (1989) closeness test. The statistic tests the null hypothesis that the two models are equally close to the actual model; against the alternative that one model is closer. This test statistic has a standard normal distribution with large positive values favouring the ZINB model and large negative values favouring the NB model(Vuong, 1989).

[66] AIC and BIC are both penalized-likelihood criteria. They are sometimes used for choosing best predictor subsets in regression and often used for comparing non-nested models, which ordinary statistical tests cannot do. The AIC or BIC for a model is usually written in the form [-2log$L$ + kp], where L is the likelihood function, p is the number of parameters in the model, and k is 2 for AIC and log(n) for BIC. AIC is an estimate of a constant plus the relative distance between the unknown true likelihood function of the data and the fitted likelihood function of the model, so that a lower AIC means a model is considered to be closer to the truth. BIC is an estimate of a function of the posterior probability of a model being true, under a certain Bayesian setup, so that a lower BIC means that a model is considered to be more likely to be the true model. BIC penalises model complexity (the number of parameters estimated) more severely than the AIC. Source: http://methodology.psu.edu/media/techreports/12-119.pdf (accessed: 29th April 2014)

[67] Manning and Bilger (2013) state that: *"When fitting an econometric model, it is well-known that we pick up part of the idiosyncratic characteristics of the data along with the systematic relationship between dependent and exploratory variables. This phenomenon is known as overfitting and generally occurs when a model is excessively*

most common model selection criteria (AIC and BIC) can be thought of as log-likelihood functions with simple penalties. They consist of a goodness-of-fit term plus a penalty to control overfitting and provide a standardised way to balance sensitivity and specificity.

Comparison of models is then extended to include logit-NB2 hurdle (HURDLENB) and finite mixture models with two components version with Poisson (FMM2-P) and NB2 (FMM2-NB2) specification. However, the limitation with all count models for the purpose of taking a 'whole system' approach is that do not account for the likely correlation (supply-side unobserved heterogeneity) between healthcare services that exists in Ireland especially for patients with cancer.

Modelling Correlated Count Data

Healthcare is not provided (or at least should not be provided) at one level in isolation to that which is provided at other levels. What happens at primary care for example, may well impact on what happens with respect to hospital services whether as a compliment or as a substitute. In modelling use of services it is important to bear in mind the potential for such connectivity and the implications it may have for estimation. Indeed it is conceivable – as others (McGregor et al., 2008) (Doherty et al. 2012) have argued that – a correlation in errors in functions estimated for different services may shed light on unobserved heterogeneity related to anxiety on the part of service users. For example, anxiety absent from a GP utilisation function may result in errors positively correlated with errors arising for the same reason in respect of function estimation for outpatient or other service utilisation.

The seemingly unrelated Poisson (SUP) model as described by King (1989) is a model for bi- or multivariate counted outcomes. Correlation between equations is introduced through a convolution structure with

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complex relative to the amount of data available. Overfitting is a major threat to regression analysis in terms of both inference and prediction".

a common additive factor (Winkelmann, 2000).[68] Major limitation of SUP model is its inability to account for over-dispersion, or extra-Poisson variation in the data. A 'seemingly unrelated negative binomial' (SUNB) developed by Winklemann (2000) generalizes the SUP model by introducing one additional dispersion parameter (which accounts for unobserved heterogeneity), the statistical significance of which can be tested by standard tests (e.g. Likelihood tests). Unfortunately, Stata code has not been developed for this model.[69] Therefore to examine the relationship between GP and hospital services of cancer survivors in Ireland, a series of bivariate probit models is employed to examine the relationship between GPs and other services.

4. Bivariate Probit Models

With bivariate probit models, it is possible to accommodate the potential unobserved heterogeneity (see earlier in this chapter, p.121/2) between utilisation of different healthcare services. In order to do this, the dependent variables are made dichotomous. In this analysis, the assumption is that a generic healthcare service (e.g. GP visit) is identified by a binary variable y_1^* and that a second generic healthcare service (e.g. hospital outpatient visit) is denoted by a binary variable y_2^*. A vector of explanatory variables, x_i, that includes types of cancer and time since diagnosis and the other sociodemographic characteristics.[70] β_i represent the coefficients to be estimated in the model and e_i represents the error term.

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[68] In Stata, Seemingly unrelated linear regression models are able to be computed with sureg command but would be of no benefit to count models needed in this analysis

[69] Contact was made with Rachel Whaley, Mark Schaffer and Maarten L. Buis who conversed on statalist in 2007 on this topic: http://www.stata.com/statalist/archive/2007-07/msg01005.html (accessed: 10th April 2014).

[70] Explanatory variables includes age, gender, employment status, marital status, education attainment, residence location, healthcare entitlements (medical card and health insurance mix), number of comorbid conditions, self-assessed health, self-assessed mental health, activities of daily living, instrumental activity of daily living.

Therefore, the first model becomes

$$y_1^* = x_1'\beta_1 + \varepsilon_1 \text{ where } y_1 = 1 \text{ if } y_1^* > 0, 0 \textit{ otherwise}$$

The second model becomes:

$$y_2^* = x_2'\beta_2 + \varepsilon_2 \text{ where } y_2 = 1 \text{ if } y_2^* > 0, 0 \textit{ otherwise}$$

The error structure captures the potential correlation between utilisation of both healthcare services can be described as:

$$\begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \end{bmatrix} \mid X \sim \mathcal{N}\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix} \right)$$

Allowing for correlation between the error terms of the two equations recognises that there may be unobservable characteristics of individuals that influence both outcomes (whether respondent goes to the GP and whether they go to other healthcare services). If there is a positive correlation in the residuals from the two functions, then that is to say that unobserved factors that are positively related to GP visits are positively related to outpatient visits. This is consistent with the interpretation that for example a patient's anxiety about their health is driving their utilisation of both types of services. A negative correlation in the residuals from the two functions is consistent with the interpretation that factors that drive utilisation of one healthcare service (e.g. GP visit) may make a respondent less likely to use another healthcare service (e.g. outpatient hospital visits) or vice versa.

Therefore, the bivariate model is analogous to the GP gatekeeping/coordinator role. The average marginal effects for the bivariate healthcare utilisation are reported.[71] This gives the impact of a change of one of the explanatory variables on the marginal probability of each outcome. The particular focus is given to the sign

[71] An analysis could be modeled using a trivariate specification that allows correlation between GP visits, inpatient stays and day procedure visits rather than two bivariate specifications. However, the computation of marginal effects under the trivariate specification is more involved (as is the interpretation of results) than in the bivariate case.

and significance of the explanatory variables and in particular the cancer variables. All analyses in this chapter were performed using Stata SE version 11.2 (Stata, College Station, TX).

Results

Descriptive Statistics

Respondents younger than 50 years of age (n=329) and those missing aspects of their demographic profiles (n=24) were also excluded, leaving an initial analytical sample size of 8,151. Of the 522 (6.3%) respondents with a history of cancer diagnosis, 512 were over-50 years of age. Compared to their peers in the sample, those with a history of cancer in Ireland are statistically significantly more likely to be older, retired, have different entitlement arrangements, have more chronic conditions, self-report to have worse physical health status and more likely to have limitations of daily living (Table 14).

Table 14: Characteristics of TILDA respondents with and without a history of cancer

Characteristic	History of cancer (N=512)	Non-cancer (N=7639)
Predisposing		
Age (y), %		
50-54	14	20
55-59	13	21
60-69	35	31
70-79	30	20
80+	8	8
Mean age (y)	65.7	63.4
Gender %		
Male	40	46
Female	60	54
Employment status %		
Employed	24	37
Retired	50	36
Unemployed/student/ Disabled/homemaker	26	27
Marital status %		
Currently married/Living with partner	67	69
Not currently married	33	31
Enabling		
Education %		
Primary education or less	33	30
Secondary education or more	67	70
Location %		
Dublin	29	23
Other town/city	28	28
Rural	44	48
Entitlements %		
Medical card only	36	32
Health insurance only	31	41
Dual cover	28	16
No cover	4	10
Need		
Number of comorbid conditions %		
0	14	22
1	27	28
2	19	22
3+	40	28
Self assessed health status%		
Excellent/very good/good	72	85
Fair/poor	28	15
Self assessed mental health status%		
Excellent/very good/good	88	90
Fair/poor	12	10
Activities of daily living%		
Has no limitation	88	92
Has at least one limitation	12	8
Instrumental activities of daily living%		
Has no limitation	90	93
Has at least one limitation	10	7

Percentages rounded to the nearest whole number.

The analytic sample of cancer survivors was further reduced to 497 as cancer survivors who reported more than one cancer diagnosis (n=6) and who reported that their cancer occurred at a time in the future (n=9) were removed.[72] Table 15 shows the type of cancer survivor by their reported time since diagnosis. Respondents with a history of oral cavity (n=7) and larynx (n=5) were included in the 'other cancers' category. Interestingly, no TILDA respondent had a history of HPV-related oropharyngeal cancer.

Table 15: Type of cancer respondents stratified by time since diagnosis in TILDA

Type of cancer	Time Since Cancer Diagnosis				
	0-1yrs (N=93)	2-5yrs (N=168)	6-10yrs (N=102)	11+yrs (N=134)	Total (N =497)
Breast	23	50	38	54	165
Prostate	20	40	18	10	88
Colorectal§	10	21	15	15	61
Other Cancers⌘	40	57	31	55	183

§ Colon and rectal cancers ⌘Includes: Malignant melanoma (skin), non-Hodgkin lymphoma & other less prevalent cancers.

Once the cancer variable is stratified by type and time since diagnosis, it is obvious that some groups have very small numbers. This limited the planned analyses on the type of cancer stratified by time since diagnosis and threw caution on the interpretation of these results.

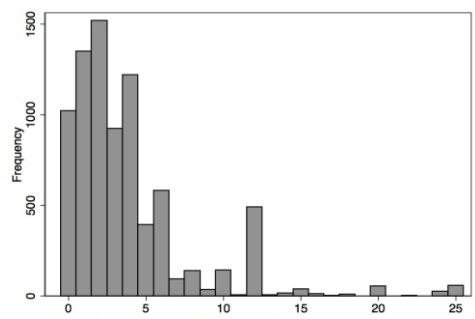
Respondents with only complete case analysis (N=8,112) of healthcare services are analysed.[73] The descriptive statistics of the healthcare services variables are given in Table 16 and shows that for all healthcare services the conditional mean and variance are not equal.[74]

[72] For example, a respondent may report to be 60 years of age and report that their age of diagnosis was 65. These respondents were removed from the analytic sample.
[73] 24 respondents were dropped – 11 missing GP visits, 7 missing emergency room visits, 3 missing daycase, 2 missing outpatient visits and 1 missing inpatient admission.
[74] Healthcare services variables had very few 'Don't Know' responds and were set to missing. GP Visits were truncated at 25. Total outpatient visits is truncated at 10. Daycase truncated at 7. Inpatient admission and emergency room truncated at 6.

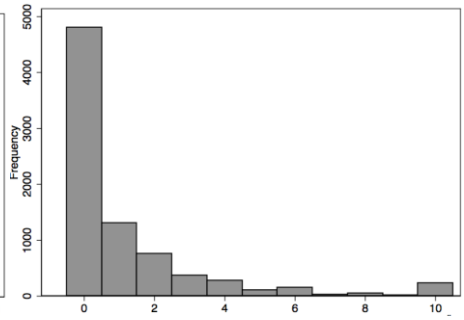
Table 16: Descriptive statistics of healthcare services in TILDA

Healthcare Service	Respondents	Mean	Std. Dev	Variance	Min	Max
GP Visits	8112	3.84	4.13	17.05	0	25
Total Outpatient Visits	8112	1.19	2.19	4.80	0	10
Office Visit	8112	0.90	1.88	3.57	0	10
Daycase Procedure	8112	0.30	0.86	0.74	0	7
Inpatient admission	8112	0.19	0.63	0.40	0	6
Emergency Room	8112	0.22	0.67	0.45	0	6
Public Services	8112	0.49	0.95	0.90	0	10

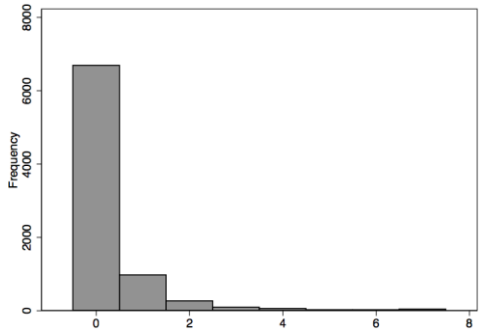
Figure 19 shows the distribution of healthcare services highlighting the variation between GP utilisation and other parts of the healthcare system. Many of the secondary care services are right skewed and have excess zeros which suggested that more sophisticated count models should be used. The distribution of the GP visits is very different – Zero observations (~12.5% of sample) and also have a number of very heavy users (>20 GP visits). As stated earlier, a clear notion of the optimal number of GP visits is not known (Nolan and Nolan, 2008) but it is advisable that healthy respondents have an annual check-up at least once a year in this age cohort.



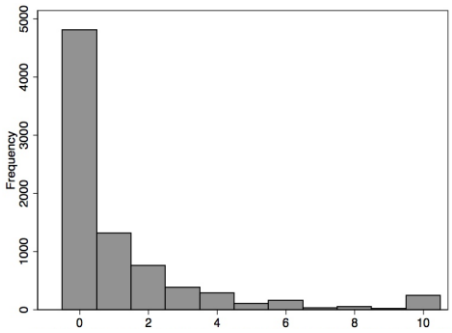
(A) GP Visits



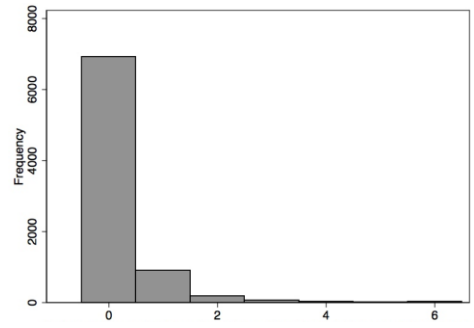
(B) Total Outpatient Visits



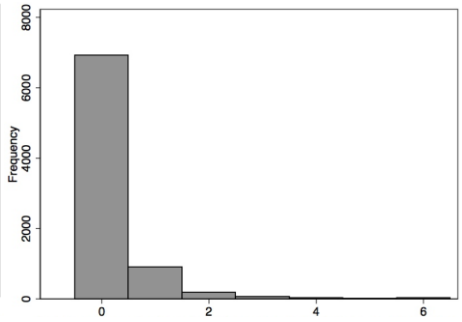
(C) Daycase surgeries



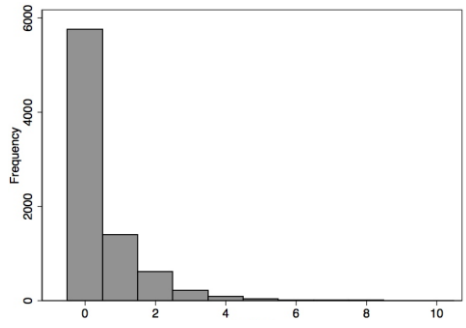
(D) Office visits



(E) Inpatient visits



(F) Emergency Room visits



(G) Public Services

Figure 19: Histograms illustrating the distribution of the number of visits per healthcare service in TILDA

As this chapter is interested in the cancer variable, the descriptive analysis stratifies cancer by type and time since diagnosis. Based on binary responses to whether a respondent used a service or not in the previous 12 months, Table 17 reveals that respondents with a history of cancer utilise healthcare services more than respondents without a history of cancer. The greatest utilisation of healthcare services is (as expected) in the time period <2 years since cancer diagnosis. Other notable points: The number of outpatients' office visits is well above those without a history of cancer but decreases the longer a respondent is a survivor. Respondents with a history of prostate cancer are the most likely to have at least 1 GP visit and 1 outpatient visit. Colorectal cancer respondents were the most likely to have an inpatient stay.

Table 17: Healthcare utilisation (≥1 service use) by time since cancer diagnosis and type of cancer

Respondents	GP %	Total Outpatient (OP)%	OP – Office visit%	OP – Daycase Procedure %	Inpatient Admissions %	Emergency Room %	Public Service %
No-cancer	86.9	39.0	30.3	16.7	12.2	14.7	28.6
0-1 years	96.8	91.4	80.7	55.9	60.2	28.0	52.7
2-5 years	95.2	69.6	56.5	30.4	16.1	16.7	37.5
6-10 years	95.1	69.6	50.0	39.2	18.6	19.6	45.1
11+ years	91.8	56.7	48.5	17.9	17.2	16.4	32.8
Breast	94.6	81.4	71.5	44.0	23.0	15.2	41.8
Prostate	97.7	93.4	69.2	62.3	21.4	18.2	34.1
Colorectal§	93.4	81.8	68.9	53.8	41.0	34.4	45.9
Other Cancers⌘	93.4	77.2	64.5	54.2	24.0	18.7	41.0

§ Colon and rectal cancers ⌘Includes: Malignant melanoma (skin), non-Hodgkin lymphoma & other less prevalent cancers.

Statistical Analyses - Count Models

In order to run and compare the Zero-inflated models, a simplified model was run owing to the fact that the models failed to converge due to the multiple maxima in the likelihood function. The parsimonious model containing age, gender, cancer stratified by time since diagnosis (as dummy variables), 1, 2 or 3+ chronic diseases (as dummy variables), whether respondent had private health insurance only, just medical card only or no cover as regressors was run. In Table 18, the preferred model for each healthcare service using the countfit program

is reported. The model depends on statistic used – BIC, AIC or Yuong. Either a NB or ZINB is preferred for specific healthcare service models.

Table 18: Count model goodness-of-fit statistics of healthcare services in TILDA

GOF Test	GP Visits	Outpatient Office Visit	Daycase	Inpatient Stay	Emergency Room Visit	Public Services
BIC	ZINB	ZINB	NB	NB	NB	NB
AIC	ZINB	ZINB	ZINB	ZINB	NB	ZINB
Yuong	ZINB	ZINB	ZINB	ZINB	ZINB	ZINB

Comparison of models is then extended to include logit-NB2 hurdle (HURDLENB) and finite mixture models with 2 components version with Poisson (FMM2-P) and NB2 (FMM2-NB2) specification using the restricted model. Table 19 & 20 shows the model specification for modelling the healthcare services of greatest interest - GP visits and outpatient office (specialist) visits.

Table 19: Goodness of fit criteria for GP visits in TILDA

	Obs	Ll(null)	Ll(model)	df	AIC	BIC
NBREG	8112	-19853.56	-18720.90	17	37475.80	37594.82
ZINB	8112	-19825.86	-18720.90	19	37479.77	37612.79
HURDLENB	8112	.	-18594.97	33	37255.94	37486.98
FMM2-P	8112	.	-18658.03	33	37382.06	37613.10
FMM2-NB2	8112	.	-18403.95	35	36877.90	37122.94

Table 20: Goodness-of-fit criteria for outpatient visits in TILDA

	Obs	Ll(null)	Ll(model)	df	AIC	BIC
NBREG	8112	-9808.60	-9501.94	17	19037.89	19156.91
ZINB	8112	-9776.86	-9498.03	19	19034.05	19167.07
HURDLENB	8112	.	-9375.05	33	18816.10	19047.14
FMM2-P	8112	.	-9648.43	33	19362.86	19593.90
FMM2-NB2	8112	.	-9397.30	35	18864.58	19109.61

According to these goodness-of-fit statistics, the hurdle model preforms the best and was used to analyse count data. The other criterion for using hurdle model is that it allows for the motivation of service use using the principal-agent economic theory. The hurdle model of healthcare utilisation is given in Table 21.[75] A positively signed coefficient in the logit model means that the corresponding regressor increases the probability that the service had been used. For example for those respondents that live in a rural location, they are statistically significant less likely to have an outpatient visit (-0.6449***) than those respondents that live in Dublin. In the second part, a positive coefficient means that, conditional on a positive count, the corresponding variable increases the value of the count. For example, those respondents that live in a rural location are less likely to have a higher number of outpatient visits (-0.1392*) than those that live in Dublin. (Owing to small sample size, only the marginal effects of GP and outpatient visits could be computed and are placed in the appendix – see Table 31)

Those with one or more chronic conditions had a significantly higher probability of visiting all healthcare services and a higher number of GP visits. Of the non-need factors, those without medical care entitlements (No Cover) had a statistical significantly less probability of accessing GP services, having a daycase operation, an inpatient stay or using public services. For the second stage, the most counterintuitive result was that those respondents from a rural location were statistically significantly more likely to have higher number of GP visits.

[75] The reference case is a 50-54 year old, male, with no cancer, not married, employed, with more than primary education, from Dublin, with dual–cover (medical card and private health insurance), no chronic diseases and excellent/very/good self-assessed health, excellent/very/good self-assessed mental health with no limitations in daily activities (ADL & IADL).

Time Since Cancer Diagnosis

Those with a cancer diagnosed within 2 years have a statistical significant higher probability of utilisation all services. With respect to the GP visits model, the results show the stratified time since cancer diagnosis variable (**in bold**) did not had a significantly higher probability of visiting their GP. However, for those diagnosed 0 to 1 years, 2 to 5 years and 11+ years have a statistically significant higher number of GP visits. With respect to outpatient's office visits, the results show that respondents with cancer had significantly higher probability of having an outpatient office visit and higher number of visits. The effect dissipates further from diagnosis but remains statistically significant for outpatient office visits.

Table 21: Hurdle model of healthcare utilisation by time since cancer diagnosis in TILDA

	(1) GP_visit	(2) Outpatient	(3) Daycase	(4) IP_Admission	(5) ED_Visit	(6) Services
Stage 1: Logit						
Age 55 to 59	-0.0152	-0.0516	0.1036	0.1021	0.0921	-0.1543
	(0.1212)	(0.0954)	(0.1116)	(0.1349)	(0.1193)	(0.1089)
Age 60 to 69	0.1027	0.1015	-0.0032	0.0967	-0.1582	-0.4173**
	(0.2114)	(0.1419)	(0.1671)	(0.1938)	(0.1803)	(0.1573)
Age 70 to 79	0.1785	-0.0597	-0.2536	0.1038	-0.4552	-0.4401
	(0.3956)	(0.2480)	(0.2908)	(0.3315)	(0.3137)	(0.2646)
Age 80+	0.2593	-0.1996	-0.8188*	-0.0179	-0.7194	-0.3864
	(0.5555)	(0.3289)	(0.3903)	(0.4356)	(0.4122)	(0.3477)
Female	0.2313**	0.0552	-0.0646	-0.1154	-0.0204	0.0710
	(0.0750)	(0.0543)	(0.0641)	(0.0743)	(0.0681)	(0.0591)
Time Since Cancer Diagnosis						
Cancer 0/1 Year ago	**1.1091**	**2.2302*** **	**1.6995*** **	**2.2367*** **	**0.5733***	**0.8261*** **
	(0.6033)	**(0.2810)**	**(0.2205)**	**(0.2279)**	**(0.2439)**	**(0.2402)**
Cancer 2/5 Years ago	**0.5760**	**0.9169*** **	**0.5697** **	**0.0279**	**-0.0617**	**0.0511**
	(0.3762)	**(0.1670)**	**(0.1771)**	**(0.2209)**	**(0.2155)**	**(0.1794)**
Cancer 6/10 Year ago	**0.5937**	**0.5889** **	**1.0210*** **	**0.1949**	**0.1153**	**0.3696**
	(0.4782)	**(0.2116)**	**(0.2135)**	**(0.2681)**	**(0.2594)**	**(0.2270)**
Cancer 11+ Year ago	**0.3476**	**0.6774*** **	**-0.0009**	**0.2747**	**0.0275**	**0.0146**
	(0.3379)	**(0.1864)**	**(0.2337)**	**(0.2411)**	**(0.2420)**	**(0.2100)**
Married/LWP	0.1318	0.0542	0.1224	-0.0202	-0.1507*	-0.1843**
	(0.0863)	(0.0587)	(0.0702)	(0.0782)	(0.0715)	(0.0608)
Retired	0.0317	0.1460	0.2253*	0.1046	0.0414	0.3495***
	(0.1126)	(0.0775)	(0.0911)	(0.1078)	(0.0987)	(0.0876)
Unemployed/ Student/Homemaker	-0.0645 (0.0987)	0.0248 (0.0747)	0.0970 (0.0888)	0.1461 (0.1052)	0.0448 (0.0942)	0.1950* (0.0836)

Primary Education Or less	-0.0098 (0.0961)	-0.1170 (0.0626)	-0.1429 (0.0747)	-0.1465 (0.0837)	-0.0394 (0.0771)	-0.2240*** (0.0652)
Town not Dublin	0.1374 (0.1008)	-0.5483*** (0.0692)	-0.1462 (0.0834)	0.1996* (0.0975)	-0.0332 (0.0865)	-0.2928*** (0.0774)
Rural	0.1404 (0.0901)	-0.6449*** (0.0632)	-0.0429 (0.0749)	0.1381 (0.0904)	-0.2126** (0.0806)	-0.3000*** (0.0709)
Medical card only	-0.2547 (0.1610)	0.1036 (0.0791)	-0.2807** (0.0930)	-0.1463 (0.0999)	0.0299 (0.0971)	0.2263** (0.0758)
Health insurance Only	-0.8172*** (0.1553)	-0.1035 (0.0842)	-0.0441 (0.0969)	-0.2233* (0.1104)	-0.1278 (0.1061)	-1.4952*** (0.0904)
No cover	-1.1581*** (0.1709)	-0.0888 (0.1137)	-0.3896** (0.1389)	-0.7995*** (0.1790)	-0.0718 (0.1424)	-1.1585*** (0.1282)
Chronic_1	0.7729*** (0.0827)	0.5094*** (0.0837)	0.4896*** (0.1041)	0.3098* (0.1239)	0.3687*** (0.1077)	0.2955*** (0.0892)
Chronic_2	1.4347*** (0.1105)	0.8401*** (0.0862)	0.7082*** (0.1069)	0.5539*** (0.1251)	0.4366*** (0.1121)	0.4693*** (0.0921)
Chronic_3	1.9559*** (0.1381)	1.3009*** (0.0845)	1.1026*** (0.1037)	0.8736*** (0.1202)	0.7559*** (0.1077)	0.7101*** (0.0892)
SAH	-1.0086*** (0.1916)	-0.6398*** (0.0754)	-0.4271*** (0.0854)	-0.7866*** (0.0912)	-0.6601*** (0.0867)	-0.2623** (0.0801)
SAMH	-0.1063 (0.1704)	0.0615 (0.0873)	-0.1490 (0.0976)	0.1251 (0.1103)	-0.1005 (0.1000)	-0.0263 (0.0922)
DISADL	0.4716 (0.2409)	0.4282*** (0.0958)	0.2901** (0.1073)	0.3140** (0.1150)	0.4025*** (0.1090)	0.5352*** (0.1015)
DISIADL	-0.0990 (0.2442)	0.1360 (0.1065)	0.2518* (0.1190)	0.3049* (0.1245)	-0.0039 (0.1228)	0.7700*** (0.1117)
_cons	1.6800*** (0.4825)	-0.7055* (0.2810)	-1.8415*** (0.3292)	-2.1502*** (0.3729)	-1.8624*** (0.3485)	-1.0270*** (0.2960)
Stage 2: Negbinomial						
Age_5559	-0.0152	-0.0678	-0.1006	0.4573	0.2277	-0.2452

	(0.0422)	(0.1019)	(0.2105)	(0.2935)	(0.2529)	(0.1293)
Age_6069	-0.1933**	-0.1089	0.0075	0.3830	-0.5959	-0.0186
	(0.0620)	(0.1476)	(0.3102)	(0.4246)	(0.3970)	(0.1633)
Age_7079	-0.3358**	-0.1847	-0.1328	0.1525	-1.1346	-0.0776
	(0.1062)	(0.2570)	(0.5111)	(0.7082)	(0.6703)	(0.2641)
Age_80	-0.3452*	-0.2360	-0.4920	0.2836	-0.9512	0.1168
	(0.1399)	(0.3382)	(0.7025)	(0.9293)	(0.8787)	(0.3347)
Female	-0.0427	-0.0814	-0.3122*	-0.3057*	-0.0414	-0.0392
	(0.0235)	(0.0563)	(0.1247)	(0.1547)	(0.1411)	(0.0590)
Time Since Cancer Diagnosis						
Cancer 0/1	**0.4985*** **	**0.7490*** **	**1.3499*** **	**0.9136** **	**0.4342**	**-0.0554**
	(0.0886)	**(0.1453)**	**(0.2825)**	**(0.3032)**	**(0.4251)**	**(0.1898)**
Cancer 2/5	**0.2745*** **	**0.5231*** **	**0.7796** **	**0.0456**	**-0.4019**	**0.1109**
	(0.0690)	**(0.1316)**	**(0.2921)**	**(0.4648)**	**(0.4771)**	**(0.1566)**
Cancer 6/10	**-0.0422**	**0.3512***	**0.4782**	**0.7418**	**0.3113**	**0.1291**
	(0.0924)	**(0.1799)**	**(0.3295)**	**(0.4959)**	**(0.5020)**	**(0.1763)**
Cancer 11+	**0.2424** **	**0.3135***	**0.7349**	**0.7729**	**0.5364**	**-0.0518**
	(0.0804)	**(0.1623)**	**(0.4058)**	**(0.4559)**	**(0.4990)**	**(0.1957)**
Married/LWP	-0.0713**	0.0037	0.0448	-0.0727	0.1329	-0.2018***
	(0.0247)	(0.0596)	(0.1325)	(0.1639)	(0.1505)	(0.0584)
Retired	0.0888**	0.3281***	0.0866	-0.1103	0.2659	0.0796
	(0.0339)	(0.0836)	(0.1740)	(0.2377)	(0.2087)	(0.1075)
Unemployed/ Student/Homemaker	0.1860*** (0.0326)	0.3130*** (0.0802)	0.1723 (0.1685)	0.1140 (0.2345)	0.1397 (0.1964)	0.0513 (0.1049)
Primary Education Or less	0.0721** (0.0260)	0.0234 (0.0642)	-0.3292* (0.1397)	-0.3532* (0.1680)	0.0527 (0.1605)	-0.0558 (0.0613)
Town	0.1291***	-0.0962	-0.0619	0.0888	0.2956	-0.0694
	(0.0311)	(0.0700)	(0.1552)	(0.2055)	(0.1869)	(0.0732)
Rural	0.1226***	-0.1392*	-0.1285	0.2476	0.3502*	-0.1336
	(0.0286)	(0.0635)	(0.1375)	(0.1900)	(0.1705)	(0.0685)

Medical card only	0.0598	-0.0371	-0.0705	0.0935	-0.3121	-0.1249
	(0.0317)	(0.0786)	(0.1646)	(0.1976)	(0.1931)	(0.0666)
Health insurance Only	-0.3740***	-0.1394	-0.2164	0.1691	-0.6322**	-0.4580***
	(0.0353)	(0.0847)	(0.1704)	(0.2292)	(0.2173)	(0.1121)
No cover	-0.4345***	-0.3112*	-0.2289	0.3640	-0.2758	-0.7656***
	(0.0511)	(0.1246)	(0.2700)	(0.3924)	(0.2898)	(0.2018)
Chronic_1	0.2767***	0.0149	-0.1829	-0.0316	0.0175	0.1156
	(0.0373)	(0.1016)	(0.2129)	(0.2702)	(0.2467)	(0.1145)
Chronic_2	0.4864***	0.0057	0.1300	-0.3413	-0.0078	-0.0017
	(0.0379)	(0.1026)	(0.2142)	(0.2723)	(0.2554)	(0.1159)
Chronic_3	0.6120***	0.1744	0.2076	-0.3467	0.3188	0.2805**
	(0.0369)	(0.0971)	(0.2040)	(0.2552)	(0.2381)	(0.1065)
SAH	-0.3915***	-0.3940***	-0.4790***	-0.7485***	-0.3761*	-0.3286***
	(0.0307)	(0.0671)	(0.1391)	(0.1756)	(0.1653)	(0.0657)
SAMH	-0.1213***	-0.0492	-0.2203	0.0137	0.0388	-0.1272
	(0.0354)	(0.0805)	(0.1659)	(0.2131)	(0.1913)	(0.0733)
DISADL	0.2332***	0.0804	0.2343	0.3699	0.0637	0.3647***
	(0.0385)	(0.0822)	(0.1728)	(0.2140)	(0.2089)	(0.0723)
DISIADL	0.1027*	0.0654	0.4379*	0.1893	0.6693**	0.3023***
	(0.0422)	(0.0916)	(0.1890)	(0.2253)	(0.2198)	(0.0755)
_cons	0.9404***	0.7803**	-2.1596	-12.1801	-13.2811	0.2658
	(0.1196)	(0.2890)	(1.6345)	(32.1922)	(10.1467)	(0.2872)
lnalpha _cons	-0.7336***	0.1945	2.7572	11.8598	12.4812	-1.5286***
	(0.0387)	(0.1131)	(1.6822)	(32.1849)	(10.1208)	(0.2701)

N	8112	8112	8112	8112	8112	8112
ll	-18314.8700	-9207.0790	-5120.0523	-3797.5247	-4342.4560	-6479.5021
aic	36739.7400	18524.1580	10350.1046	7705.0493	8794.9121	13069.0042
bic	37124.8004	18909.2185	10735.1651	8090.1098	9179.9725	13454.0647

Coefficients of models are given with standard errors in parentheses.
* p<0.05, ** p<0.01, *** p<0.001

An alternative way of presenting the results is by using incidence rate ratio (IRR) (Table 22). The IRR represents the change in the dependent variable in terms of a percentage increase or decrease; with the precise percentage determined by the amount the IRR is either above or below 1. For certain audiences, this may more clearly communicate independent variable influence then the regression coefficients. For example, compared to a respondent without cancer, a respondent that was diagnosed with cancer 11+ years ago visit outpatients some 96% more than a respondent that has never had a cancer diagnosis *ceteris paribas*. In other words, a respondent having had a cancer diagnosis 11 + years ago is almost twice as likely to have an outpatient visit compared to a respondent without a cancer diagnosis, *ceteris paribas*.

Table 22: Hurdle model by time since cancer diagnosis, Incidence Rate Ratio

IRR	**GP**	**Outpatient office visit**	**Daycase**	**Inpatient**	**Emergency Room**	**Public Services**
No Cancer	REF	REF	REF	REF	REF	REF
0/1years	3.03	9.30***	5.47***	9.36***	1.77***	2.28***
2/5years	1.77	2.50***	1.76***	1.02	0.94	1.05
6/10 years	1.81	1.80***	2.77***	1.31	1.12	1.44
11+years	1.41	1.96***	1.00	0.98	1.02	1.01

*** **<0.001** *<**0.05** IRR – Incidence rate ratio. Full model contains all the variables in Table 21

In conclusion, these results seem to suggest that those respondents with a history of cancer have a higher probability of seeking specialist care and have higher count of outpatients' visits. This effect is strongest closer to the time of diagnosis. Although, cancer survivors do not have a higher probability of attending a GP visit, once engaged they have a higher count of GP visits.

Type of Cancer

Using the same hurdle model of healthcare utilisation in Table 21 but stratified by type of cancer instead of time since cancer diagnosis is given in the appendix (p.219-22). For brevity, only the IRR of the 1st part of the model is reported here (Table 23) along with NB2

coefficients of the 2nd part of the model. The interpretation of the IRR coefficients is again - Compared to a respondent without cancer, a respondent that was history of breast cancer visits outpatients some 180% more than a respondent that has never had a cancer diagnosis *ceteris paribas.* In other words, a respondent having had a breast cancer diagnosis are 2.8 times as likely to have an outpatient visit compared to a respondent without a cancer diagnosis, *ceteris paribas*.

Table 23: Hurdle model of healthcare utilisation by cancer type, incidence rate ratio (IRR)

	GP	Outpatient office visit	Daycase	Inpatient	Emergency Room	Services
1st Part, IRR						
No Cancer	REF	REF	REF	REF	REF	REF
Breast	1.71	2.80***	2.08***	1.88***	0.88	1.42*
Prostate	3.88	3.68***	1.31	1.29	1.05	1.01
Colorectal§	1.07	4.31***	3.60***	3.71***	2.47***	1.33
Other Cancer⌘	1.71	1.91***	2.38***	1.84***	1.07	1.31
2nd Part NB2, coeff						
Breast	0.19***	0.54***	0.61*	1.04***	-0.05	0.05
Prostate	0.38***	0.50***	1.21***	0.57	0.62	0.08
Colorectal	0.36***	0.63***	0.68	0.48	-0.04	0.15
Other Cancer	0.21***	0.45***	1.12***	0.59	0.39	-0.02

***** <0.01 *<0.05** Full Model contains all the variables in Table 21.§Colon and rectal cancers. ⌘Includes: Malignant melanoma (skin), non-Hodgkin lymphoma & other less prevalent cancers.

These results seem to suggest that those respondents with a history of cancer, regardless of type, have a higher probability of seeking specialist care. Colorectal cancers have a 147% increase probability of attending an emergency room and Prostate cancer is the least likely to have an inpatient admission. Conditional on a positive count, all cancer types statistically significantly increase the value of the count of the positive visits to the GP.

Bivariate Probit Model

In Table 24, the average marginal effects for the bivariate healthcare utilisation models are presented. While GP visits are included in all bivariate models, the marginal effects for GP visits are presented from

the model with outpatient office visits only.[76] From Table 24 it is evident that those diagnosed within 2-years had significantly higher probability of having contact with all facets of the healthcare system. It is intuitive to think that those with a recent history of cancer utilise secondary healthcare services more. All cancer patients have a significantly higher probability of having an outpatient visit. The interpretation of the marginal effect coefficients is that the probability of an outpatient office visit is 17.7 percentage points higher for those 2-5 years after their cancer diagnosis, 11.5 percentage points higher and 13.0 percentage points higher, respectively, for those 6–10 years and 11 years or more after their cancer diagnosis than respondents without a history of cancer. As bivariate probit regression model corrects for correlation in errors, more confidence can be given to estimate level of service use post diagnosis than in the count models where this type of unobserved heterogeneity has not been corrected.

The correlation in the errors (σ) is statistically significant and positive between GP and other healthcare services.[77] The correlation is highest among GP and outpatient visits and lowest between GP and public services.[78] This correlation is to say that where the GP function under or overestimates the use of GP visits, that the second function (e.g. inpatient admission) also either under or overestimates the use of this service. A suggestive interpretation is that 'worried' respondents (who cannot be directly identified using observed variables) are more likely

[76] The reason for this is that the coefficients for GP visits between bivariate probit models are not significantly different from each other.

[77] If the GP function overestimates GP visits and underestimates hospital visits there will be a negative correlation in residuals or if the GP function underestimates GP visits and hospital function overestimates hospital visits will also have a negative correlation. If the GP function overestimated GP visits and hospital visits, there will be a positive correlation in residuals from the two functions; Suppose the GP and/or the patient is anxious about their health – cannot observe anxiety - but the individual may be more likely to visit the GP than the model predicts – therefore underestimating visits to the GP and get a negative residual AND the GP may be more likely to refer the person onto hospital – the model underestimates hospital use and again you get a negative residual. The two negative residuals give you positive correlation in residuals.

[78] Therefore you don't get the same degree of overuse or underuse of public services.

to visit their GP and hospital services. Equally though it may be that, GPs may be risk averse and are more likely to refer worried patients onto to hospital services – though this might run counter to the notion of the GP as gatekeeper to other services.

In appendix (P.223/24) the results of the type of cancer stratified by time since cancer diagnosis is given. Unfortunately, the low incidence of some cancers makes the results unreliable for interpretation. While the results with respect to other variables included in the functions are not the focus of this chapter, it is noteworthy that they are moderately consistent with expectations in terms of the signs and significance of estimated marginal effects and with the findings of others (Doherty et al., 2013). Respondents without a medical card or private health insurance (No cover) are significantly less likely to visit their GP than those who do have the enhanced access these confer. Women are significantly more likely to visit their GP than men. Also, those with poorer self-assessed health or have 1 or more chronic conditions are also more likely to visit their GP. Rather surprisingly the results do not show any effect for age, marital status, education or location on GP utilisation.

For hospital services functions were estimated for outpatient office visits, daycase, inpatient stays and emergency room visits. In terms of inpatient stays the marginal effect representing the newly diagnosed category (<2 years) is positive and significant. Similarly the results show that whilst those individuals with a history of cancer have a higher propensity to have an outpatient visit, the relationship with daycase is weaker. Fewer of the other independent variables appear significant for hospital inpatient stays compared to the GP visits. Again this is consistent with intuition and likely reflects the greater role accorded to the referring or admitting physician in the decision to access inpatient care than the respondent whose characteristics are explicitly modeled.

A surprising finding is that private insurance is not a significant determinant of inpatient stays. It may be that private health insurance does not increase the likelihood of a person accessing care; it could impact on the speed and length of stay with which care is accessed, which is not observable in a bivariate probit model. As can be seen with hospital daycases, those with no cover or just a medical card were statistically significant less likely to have had a procedure compared to respondents with dual cover or with just private health insurance. Having one or more chronic conditions significantly increases the probability of using healthcare services. The trend in probability of healthcare utilisation increases with the number of chronic comorbid conditions. Interestingly those in rural areas and outside Dublin are less likely to have outpatient visits and use public services such as physiotherapy or home help.

Table 24: Bivariate probit models for healthcare utilisation

Characteristic	GP Visits	Outpatient Office Visit	Outpatient Daycase	Inpatient Stay	Emergency Room Visit	Public Services
No Cancer	***REF***	***REF***	***REF***	***REF***	***REF***	***REF***
Time since cancer diagnosis:						
0-1 year	0.086	0.424***	0.248***	0.253**	0.075**	0.138***
	(0.047)	(0.049)	(0.032)	(0.026)	(0.044)	(0.038)
2-5 years	0.050	0.177***	0.083***	0.006	-0.009	0.008
	(0.032)	(0.032)	(0.025)	(0.023)	(0.026)	(0.030)
6-10 years	0.054	0.115***	0.146***	0.020	0.013	0.066
	(0.041)	(0.042)	(0.031)	(0.029)	(0.032)	(0.037)
11+ years	0.033	0.130***	0.002	0.030	0.005	0.005
	(0.031)	(0.036)	(0.031)	(0.026)	(0.030)	(0.034)
Age						
50-54 years	REF	REF	REF	REF	REF	REF
55-59 years	0.007	-0.012	0.015	0.012	0.010	-0.004
	(0.011)	(0.016)	(0.015)	(0.012)	(0.013)	(0.016)
60-69 years	0.039***	0.018	0.002	0.012	0.003	-0.022
	(0.011)	(0.016)	(0.014)	(0.012)	(0.013)	(0.016)
70-79 years	0.053***	-0.013	-0.032	0.014	-0.008	0.017
	(0.015)	(0.020)	(0.017)	(0.015)	(0.016)	(0.019)
80+ years	0.061***	-0.037	-0.104*	0.004	-0.030	0.061**
	(0.019)	(0.025)	(0.018)	(0.018)	(0.018)	(0.025)
Gender						
Male	REF	REF	REF	REF	REF	REF
Female	0.017**	0.008	-0.007	-0.009	-0.006	0.014
	(0.007)	(0.011)	(0.009)	(0.008)	(0.009)	(0.010)

Employment Status						
Employed	REF	REF	REF	REF	REF	REF
Retired	0.005	0.026*	0.033***	0.011	0.010	0.053***
	(0.011)	(0.015)	(0.012)	(0.011)	(0.012)	(0.014)
Other	-0.001	0.003	0.013	0.008	0.004	0.029**
	(0.010)	(0.014)	(0.012)	(0.011)	(0.012)	(0.014)
Marital status						
Not Currently married	REF	REF	REF	REF	REF	REF
Currently married/Living with partner	0.014*	0.012	0.016	-0.006	-0.023**	-0.031***
	(0.008)	(0.012)	(0.100)	(0.008)	(0.009)	(0.010)
Enabling						
Education						
Less than primary	REF	REF	REF	REF	REF	REF
Primary education or more	-0.003	-0.020*	-0.015	-0.013	0.000	-0.034***
	(0.009)	(0.012)	(0.010)	(0.009)	(0.009)	(0.014)
Location						
Dublin	REF	REF	REF	REF	REF	REF
Other town/city	0.008	-0.106***	-0.027**	0.022	-0.011	-0.045***
	(0.010)	(0.013)	(0.012)	(0.010)	(0.012)	(0.013)
Rural	0.011	-0.123***	-0.016	0.013	-0.033***	-0.046***
	(0.009)	(0.011)	(0.011)	(0.009)	(0.011)	(0.012)
Entitlements						
Dual Cover	REF	REF	REF	REF	REF	REF
Medical card only	-0.017	0.018	-0.157***	-0.016	0.003	0.379***
	(0.013)	(0.015)	(0.053)	(0.011)	(0.011)	(0.012)
Health Insurance only	-0.073***	-0.020	-0.028	-0.024	-0.015	-0.237***
	(0.013)	(0.016)	(0.055)	(0.011)	(0.0.12)	(0.014)
No cover	-0.106***	-0.020	-0.221***	-0.077***	-0.009	-0.187***

	(0.106)	(0.021)	(0.076)	(0.017)	(0.017)	(0.019)
Need						
Number of comorbid conditions						
0	REF	REF	REF	REF	REF	REF
1	0.079***	0.096***	0.054***	0.031***	0.043***	0.041***
	(0.012)	(0.013)	(0.011)	(0.010)	(0.012)	(0.014)
2	0.138***	0.159***	0.078***	0.056***	0.051***	0.069***
	(0.010)	(0.015)	(0.012)	(0.011)	(0.012)	(0.015)
3+	0.176***	0.250***	0.141***	0.092***	0.091***	0.111***
	(0.012)	(0.015)	(0.013)	(0.011)	(0.012)	(0.015)
Self-Assessed Health						
Fair/poor	REF	REF	REF	REF	REF	REF
Excellent/very good/good	-0.082***	-0.125***	-0.056***	-0.085***	-0.084***	-0.042***
	(0.015)	(0.015)	(0.012)	(0.012)	(0.011)	(0.014)
Self-Assessed Mental Health						
Fair/poor	REF	REF	REF	REF	REF	REF
Excellent/very good/good	0.012	0.012	-0.021	0.013	-0.013	-0.006
	(0.015)	(0.018)	(0.014)	(0.011)	(0.013)	(0.016)
Activities of daily living						
Has no limitation	REF	REF	REF	REF	REF	REF
Has at least one limitation	0.084***	0.084***	0.029*	0.035**	0.052***	0.096***
	(0.018)	(0.020)	(0.016)	(0.013)	(0.014)	(0.018)
Instrumental activities of daily living						
Has no limitation	REF	REF	REF	REF	REF	REF
Has at least one limitation	-0.017	0.025	0.034*	0.035**	0.003	0.130***
	(0.021)	(0.022)	(0.017)	(0.014)	(0.016)	(0.019)

N	8112	8112	8112	8112	8112
σ (GP, healthcare service)	0.301***	0.274***	0.287***	0.243***	0.102***
	(0.030)	(0.035)	(0.042)	(0.036)	(0.031)
Log-likelihood	-7121.23	-6115.55	-5418.28	-5825.96	-6571.17

*** <0.01 ** <0.05 *<0.1 Estimates presented are average marginal effects. Estimates in brackets are the standard errors.

σ = correlation in error terms

Discussion

Earlier chapters have shown that the profile of the economic burden of HNC is conditional upon the HPV status. Those that have HPV-related HNC are likely to live for many years after their initial diagnosis. The likely increase in healthcare utilisation of HPV-related HNC and other cancer survivors in general will add considerable strain to the Irish healthcare system. In Ireland, 85% of cancers are diagnosed in people over 50 years of age (NCRI, 2013), making TILDA a suitable dataset to investigate the healthcare utilisation levels of respondents with a history of cancer.

In this analysis, a menu of count models was assessed before a bivariate probit analysis was undertaken. Negative binomial count models have been previously used to (i) investigate the healthcare use of osteoarthritis and rheumatoid arthritis (Doherty and O'Neill, 2013) and (ii) in the main TILDA patterns and determinants of healthcare utilisation report (McNamara et al., 2013).[79] However, using information criteria (AIC and BIC), a hurdle model was deemed to be the preferred count model and is a better reflection of principal-agent economic theory. In the literature, it is not unusual for different models to perform better for different services. Jimenez-Martin et al. (2002) showed that the finite mixture model performs better for the visits to GPs while the hurdle model is preferred for specialists.

It appears from the hurdle count model that respondents with a history of cancer (many years after cancer diagnosis) utilise outpatient office visits significantly more than respondents without a history of cancer. This is an interesting point that was complimented with a bivariate probit model to account for the relationship between GPs and

[79] This report states that with respect to healthcare utilisation the key drivers are poor self-rated health, limitations of daily activity, presence of one and more chronic conditions and entitlement status (McNamara et al., 2013). These explanatory variables in the hurdle and bivariate models are consistent with expectations in terms of the signs and significance of estimated marginal effects in the Irish context.

other healthcare services. The correlation in the error terms of the bivariate models is positive and statistically significant.

Given this positive correlation, there is an unobserved characteristic that is influencing utilisation of both GP and other healthcare services. An intuitive explanation is that unobserved heterogeneity may be evident both among the respondents and their GPs given the latter's role in referring the respondent on to subsequent hospital care. While this explanation 'fits' the results and indeed offers an explanation for variations in the degree of correlation evident between services – respondents are likely to be less anxious about use of dietician than outpatient specialist care - the nature of unobserved heterogeneity could also be preference related, that is, those with a greater taste for healthcare may use more than the model based on observable characteristics predicts whether in respect of GP or other services. The likelihood is that it is a combination of these and maybe other healthcare structural factors.

Comparison to Other Healthcare Systems

It is likely that the make-up of the healthcare system influences how survivorship care is delivered. In the Netherlands, where there is mandatory insurance of all inhabitants for standard medical care and every citizen is listed with a GP (Schäfer et al., 2010), the influential document *'cancer survivorship care'* recommends that when no sign of recurrence or ill-health effects after 1-year the patient be referred back to the GP (Oncoline, 2011). This is confirmed by a study that shows that GP use by patients with breast, prostate and colorectal cancer increased 2-5 years post diagnosis by 24%, 33% and 15% respectively, compared with controls (Heins et al., 2012).

In the UK, breast and colorectal cancer survivors had one more consultation per year compared with controls up to 5-years after diagnosis, with rates converging at 10 years post-diagnosis (Khan et al., 2011). This study also noted that prostate cancer survivors

consistently consulted up to three more times per year than controls and therefore leading to an impact on GP service capacity there (Khan et al., 2011). In the US, approximately 70% of breast cancer survivors have had at least one visit to their oncology specialist 1-year after active treatment had concluded (Snyder et al., 2009). [80]

The analysis in this chapter is the first time that the healthcare utilisation of cancer survivors in Ireland has been examined. Based on the Andersen Model of healthcare utilisation, newly diagnosed cancer survivors in TILDA have a higher probability of using more healthcare services than those without a history of cancer accounting for predisposing, enabling and other need factors. However, it is what happens after the initial post-treatment phase that is of significant importance to capture for policy-makers. This analysis suggests that respondents with a long history of cancer are probable still seen in secondary care. The empirical analysis (especially the bivariate models) suggests that the role of GPs may not be well defined in Ireland with respect to the management of cancer survivors and warrants further investigation. Concerns do exist about the adequacy of the supply of GPs and practice nurses in Ireland to cope with increased demand of other chronic conditions (Teljeur et al., 2014).

A research proposal to aid GPs is to evaluate survivorship care plans (SCPs). These are personalised documents presented to cancer patients at the end of treatment that summaries key aspects of cancer treatment and recommend appropriate ongoing medical care and self-management (IOM, 2005). However, SCPs may not be the panacea for all cancer survivors. As demonstrated in a recent randomized controlled trial in Canada, SCPs were deemed not to be cost-effective in breast cancer patients (Coyle et al., 2013). For cancer policy-makers, survivorship planning ought to be a matter of urgency to strategically

[80] ASCO guidelines made reference to continuation of care by PCPs and state that there is neither any difference in outcomes when compared to follow-up by hospital specialists nor any difference in patient satisfaction between the two.

deliver safe, efficient and cost-effective care for this burgeoning population in a bid to control costs and to manage expectations

Limitations of Analysis

A number of limitations must be borne in mind with this analysis. TILDA is a household survey of community dwelling adults and responses are subject to recall bias. Detailed information about cancer stage or other tumour characteristics are not collected and information about specific treatments is limited. Seriously ill individuals, those with rare cancers or short duration (e.g. lung cancer) may be less likely to respond to this survey. This survivorship bias is a form of selection bias. This will distort the generalizability of the results of healthcare utilisation to all cancer survivors. A similar study in the US using MEPS showed that the respondents of these surveys who are identified as cancer survivors mainly consist of long term survivors of common adult cancers (e.g. breast and prostate), often participating many years after their cancer diagnosis (Yabroff et al., 2012). The prevalence of these survivors in our data is simply an epidemiological fact. Therefore, the results of this study are not generaliseable to other community dwelling cancer survivors in the age groups captured in TILDA. When stratified by cancer type, the sample sizes by time period are small (N<55) and thus make inferences about service use somewhat unreliable. Perhaps, the biggest limitation with this analysis is the fact that disease-specific healthcare utilisation data was not ascertained.

Future Research

Building on this work, future research could include detailed analyse of inpatient and outpatient hospital data of long-term cancer survivors available from the National Casemix Programme. This would confirm or refute the suspicions that long-term cancer survivors' cancer care is still being predominately monitored or coordinated in secondary care. Research to see if the capacity and funding of primary care to accommodate the extra cancer survivors is also needed. This would

also accommodate the choices of the patients to have their survivorship care predominately with their GP.

Conclusion

The various analyses from the TILDA dataset show that healthcare utilisation of cancer survivors over 50 years of age is significantly different from those without a history of cancer. The bivariate probit analysis suggests that the level of follow-up and management of respondents with a history of cancer is predominately in secondary specialist care. This is very different to the provision of survivorship care in the Netherlands and the UK. The rising prevalence, the limited number of oncology services and the extra demand for survivorship care will have resource implications for cancer policy-makers in Ireland. A suggestion is to develop capacity in primary care for managing individuals with a history of cancer. An update of the National Cancer Control Programme (NCCP) national strategy to include the care of long-term survivors is warranted. A plan similar in outlook to the latest IOM report in the US would be very welcomed in Ireland (IOM, 2013).

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Chapter 6: Cancer Communication – An Economic Perspective on Health Literacy

To win the so-called '*war on cancer'*, public health authorities ought to be cognizant of the importance of effective cancer communication. For prevention of HPV-related HNC, strategies are the needed to increase awareness of this emerging cancer and the potential of HPV vaccination to reduce the burden (characterised in chapter two and three). At the heart of this communication 'battle' is closing what economists call the 'information asymmetry' gap between informed healthcare professionals and the public.[81]

The fundamental concept that underpins any good cancer communication strategy is 'health literacy'.[82] A term that has come to mean different things to various audiences and is a source of considerable confusion and debate (Baker, 2006). A recent systematic review identified 17 definitions and 12 conceptual models (Sørensen et al., 2012). Parker (2009) provides a useful conceptual framework (Figure 20) to discuss health literacy: *"One must align skills and abilities [of individuals] with the demands and complexity of the system. When that is accomplished, one has health literacy"*.

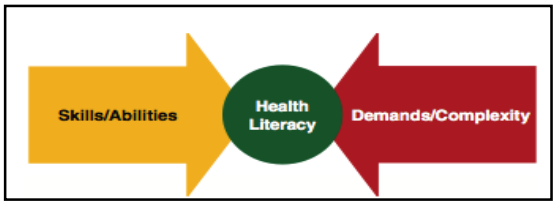

Figure 20: Health literacy framework (Parker, 2009)

[81] The definition of asymmetric information – situations where one economic agent knows something that another economic agent doesn't.

[82] Cancer communication has been defined as: Translating theoretical (imprecise and incomplete) and changing knowledge of causality, risk, prevention and management of cancer has developed into its own body of knowledge often termed 'cancer communication' (Ratzan, 2009).

In the analysis of the healthcare utilisation of cancer survivors, unobserved heterogeneity was a factor that needed to be considered. It is conceivable that individual's skills/abilities to navigate the healthcare system are different; it is therefore plausible to think of this side of the health literacy framework as a latent variable in any healthcare utilisation analysis. Perhaps, the most amenable action a policy-maker can take is to lessen the demands/complexity of the healthcare system.

Illiteracy is still a critical economic and health care problem in many developed countries. People with low health literacy are more likely to report poor health, have an incomplete understanding of their health problems and available treatments, and are at greater risk of hospitalisation (Pawlak, 2005). Economics can contribute to the field of health literacy and health literacy to economics. For example, health literacy can help identify the nature of barriers to health care use. Equally economics can help identify the impact of illiteracy on health and well-being motivating a search for strategies and incentives to address the issue.

Objective of Chapter

The objective of this chapter is to use an economic lens to highlight the importance of health literacy in delivering cancer control strategies. This chapter starts with a succinct review of the public's awareness of HPV as a carcinogenic. Then, pertinent economic theory is applied to the health literacy framework. Subsequently, empirical analysis using Irish data {Survey of Lifestyle, Attitudes and Nutrition (SLAN)} examines the socioeconomic gradient of the demand for a health literate healthcare system using regression and inequalities approaches. Finally, policy recommendations for improving the healthcare system and cancer communication are made.

6.1 Literature Review of HPV Awareness & Knowledge

Numerous systematic reviews have been conducted on aspects of awareness of HPV (Trim et al., 2012)(Klug et al., 2008) and acceptability of the HPV vaccination (Kessels et al., 2012)(Brewer and Fazekas, 2007). An international systemic review (2013) of girls' and parents' information needs, views and preferences about HPV vaccination concluded that many girls and their parents had limited understanding of HPV's role in cervical cancer and that impinges on their ability to make informed choices about HPV vaccination and cervical cancer screening (Hendry et al., 2013). Percentages vary from 13 to 93% on the proportion of survey participants from who had even heard of HPV (Klug et al., 2008).[83] There are many reasons for the poor awareness of the virus includes respondents struggling to interpret limited information about HPV and cancer (Hendry et al., 2013). In the US, Licht et al. (2010) also found that regardless of vaccine status, respondents lacked knowledge about the link between HPV and genital warts, about HPV transmission and the fact that HPV infection is as common in men as in women. A fifth of HPV vaccinated women in a survey in England reported that they were unaware of the virus and approximately half of the survey participants knew that HPV causes cervical cancer (Bowyer et al., 2013). The only meta-analysis to date of male views on vaccination, found that HPV awareness (defined as having heard about HPV) and HPV knowledge (defined as correctly answering questions about HPV) were positively associated with HPV vaccine acceptability (Newman et al., 2013).

Nationally Representative Data

In the US, the Health Information National Trends Survey (HINTS) was designed as a key initiative to support the NCI's mission by providing a means to systematically evaluate the public's knowledge, attitudes, and

[83] From various geographic regions in the timeframe 1992 to 2006

behaviours relevant to health communication, which have not been studied adequately through other nationally representative data collection efforts (Nelson et al., 2004). It was found that seeking cancer information is highest among females, younger respondents, those with higher education, those with higher incomes, and those with a usual source of healthcare (i.e. a primary care physician) (Rutten et al., 2006). With regards HPV, the awareness of the virus did increase between 2005 and 2007 by over 26% (Figure 21) after the introduction of the HPV vaccination to the US market in 2006.

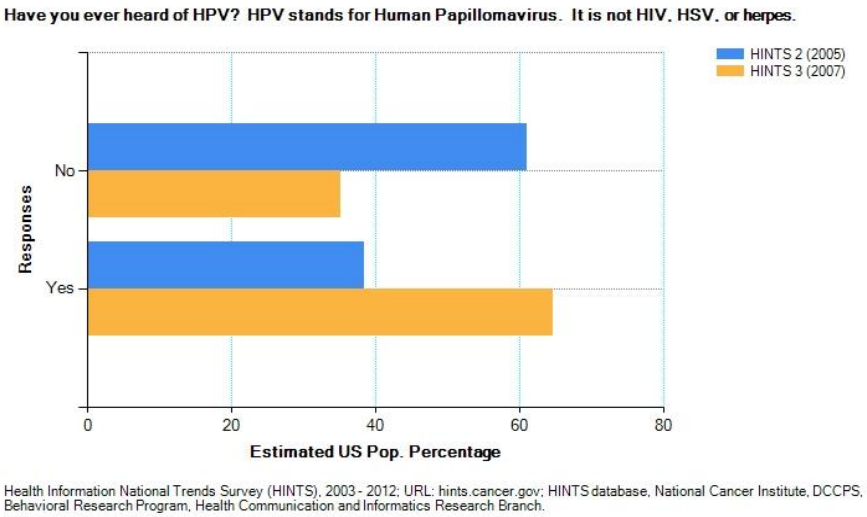

Figure 21: Have you ever heard of HPV? (HINTS 2005 & 2007)

Numerous HPV knowledge questions have been asked in various iterations of the HINTS survey- For example in 2007, the following questions were asked:

- Do you think HPV causes cervical cancer? 78.3% answered correctly.
- Do you think that HPV infection is rare? 69.6% answered correctly.

- Do you think that you can get HPV through sexual contact? 67.3% answered correctly. [84]

In the UK, the Office of National Statistics (ONS), have twice conducted cancer awareness sections of their opinions survey (October/November 2008 and October/November 2010) and asked respondents - How much do you agree that infection with HPV can increase a person's chance of developing cancer? (5-point likert scale: strongly disagree to strongly agree). [85] In 2010, over 75% of respondents either answered *'Don't Know'* or *'Not Sure'*. In general as well as in cancer communication of HPV-related cancers, policy-makers ought to cognizant of health literacy principles. The economic arguments for doing this are outlined in the next sections.

[84] http://hints.cancer.gov/topic.aspx?section=Cervical+Cancer(accessed: 20th February 2014)

[85] Surveys available at: http://discover.ukdataservice.ac.uk/series/?sn=2000043 (accessed: 15th April 2014)

6.2 Health Literacy – Skills and Abilities of Individuals

Viewed through the economic lens, health literacy is essentially about closing the knowledge gap between the agent (i.e. policy-maker, healthcare professional) and the principal (i.e. patient or parent). As economics is the study of choice, altruistic health service researchers and health economists instruct policy-makers to *nudge* individuals to make perceived healthier choices such as participation in cancer screening or availing of HPV vaccination. This approach is intended to avoid the consequences of poor choices that result in greater health expenditures, higher number of healthcare services contacts and negative externalities upon the wider society. [86]

Good Health Though Better Health Literacy

One of the most influential theoretical models in health economics is the Grossman (1972) demand for health model, which predicts that individuals with more education and health knowledge unambiguously demand more health. [87] The argument that could be made is that Grossman's conceptual model uses 'education' as a proxy for a 'health literate' individual. The model is ambiguous in predicting an educated person's derived demand for preventive healthcare - Educated individuals could both demand and utilise more preventive healthcare (because they are investing in their health stock) demand or utilise less preventive healthcare (because they are more efficient users of the preventive healthcare already received).

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[86] An externality or transaction spillover is a cost or benefit, not transmitted through prices, incurred by a party who did not agree to the action causing the cost or benefit. An example of a negative externality is that if an individual didn't avail of HPV vaccination and that tax-based funds are used to pay for the downstream consequences of treating HPV-related diseases.

[87] The main purpose of Goodman's paper was to construct a model of the demand for the commodity 'good health'. This concept of producing good health by investing in one's self is termed *health capital production*. The central proposition is that health can be viewed as a durable capital stock that produces an output of healthy time. A person determines his optimal stock of health capital at any age by equating the marginal efficiency of this capital to its user cost in terms of the price of gross investment. The model is not without its critics that highlight that the model is deterministic including the choice of when to die!

Individual Cost/Resource Utilisation in Health Literacy Studies

Individuals are described in the literature as having low, below basic, inadequate, basic, functional, intermediate, adequate, or proficient health literacy (Berkman et al., 2011). These terms are specific to the context and to the health literacy measurement tool used. Such terms underline the lack of standardisation in the field, thus making comparison of the economic burden of low health literacy across populations difficult.

Several conceptual models exist that link health literacy to health outcomes (Baker, 2006), health status (37), and healthcare utilisation (Paasche-Orlow and Wolf, 2007). Cho et al. (2008) conducted path analyses, which focuses on examining the web of relationships among measured variables;[88] whereas Bennett et al. (2009) discussed mediating effects associated with the health literacy variable and preventive health behaviours. Only a couple of studies (Howard et al., 2005)(Weiss and Palmer, 2004), have looked at the cost or healthcare utilisation of those deemed to be of limited health literacy compared to those with adequate health literacy. Those studies have insufficient strength of evidence and as Eichler et al. (2009) noted in their systematic review, these cost studies varied widely in methodological quality.[89]

Finally, Berkman et al. (2011) updated and rigorous systematic review on health literacy interventions and outcomes, suggested that health literate individuals are more efficient users of healthcare services than those with limited health literacy. The important explanatory factors include health-related knowledge, self-efficacy, and beliefs - such as stigma related to one's disease.

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[88] Examines the effects of health literacy on health status and health care utilisation while controlling for obvious confounders (i.e., gender, race, education attainment)

[89] Technical econometric issues persist in the analysis of costing data (See chapter 4). For example, results using mean costs may not give a complete picture. Additionally, in order to make robust estimates of costs attributable to one's health literacy level, the issue of confounding must be considered which was not the case.

6.3 Demands/Complexities of the Healthcare System

The other side of the health literacy framework is the healthcare system. This side can be considered to be composed of three distinct groups: payers, healthcare providers, and policy-makers. All three groups are faced with the similar dilemma of obtaining value for the money for their investments while meeting the needs of their users. Establishing the nature and burden of low health literacy in a jurisdiction is often required before addressing it.

In the only systematic review on the costs of limited health literacy, Eichler et al. (2009) reported that (a) the prevalence of limited health literacy is considerable (range 34–59%) and (b) on the health system level the additional cost of limited health literacy ranges from 3 to 5% of the total health care cost per year. The limited evidence suggests that the central issue for third-party payers (e.g., health insurers and publicly-funded healthcare systems) is that individuals who do not understand and cannot act on the medical information and instructions are likely to be more costly and less adherent to medical advice.[90] It makes economic sense that third-party payers assist their customers into proactively making healthy lifestyle decisions (such as weight loss or vaccination) in a bid to avoid reactive medical care procedures and medical costs.[91]

For the private health insurers, efficiency gains, cost containment, and profit are goals that influence decisions about how to package a health

[90] States like Missouri, Wisconsin and Iowa have reported estimates the burden of low health literacy. At a national level, for 1998, the estimated percentage of healthcare expenditures due to low health literacy is 3.2 to 7.6% in the US (Friedland, 1998)

[91] Having lower premiums and making certain preventive healthcare available without co-pays could achieve this. However, historically in the US, many individuals/families switch their health insurance plans every few years, which is a disincentive for insurers to invest in preventive medicine. The new healthcare reform mandates health insurers to cover certain preventive healthcare such as cancer screening.

insurance plan.[92] In a public healthcare setting, similar goals exist (though perhaps expressed somewhat differently in terms of obtaining value for money or delivering care in a cost-effective manner) with the added dimension of equity.[93]

Within economic theory, the concept of market failure describes the scenario when the allocation of goods and services by a free market is not efficient. Information asymmetry is an often-cited reason for market failure and central to the health literacy framework. This is the reason for government intervention in particular markets such as public health issues and vaccination.[94] Another reason, articulated by Joseph Stiglitz (1999), is that knowledge is a 'global public good' - non-rival and non-exclusive, available around the world - and that the State and global agencies must play some role in the provision of such goods.[95] The other pertinent economic theory is that of bounded rationality - the notion that in decision-making, rationality of individuals is limited by the information they have, the cognitive limitations of their minds, and the finite amount of time they have to make decisions. All things considered, the State ought to play a role in health literacy and one of the most fundamental questions regarding health literacy is how? Should policy-makers view health literacy as a health inequality, social disparity, or a public health issue? These approaches are not mutually exclusive but motivate the topic differently and impact upon the economic perspective.

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[92] It should be noted that an organization called America's Health Insurance Plans have created a task force on health literacy. An example of their commitment to the easing of the demands placed upon individuals is a checklist of reader- and user-friendly web design for health plans. These are encouraging signs in helping consumers navigate the health care system and insurers may see a reduction in unnecessary costs.

[93] Hasnain-Wynia and Wolf (2010) considered the case of health literacy as the missing link in the efforts to redress inequities in healthcare.

[94] Geoffard and Philipson (1997) illustrated that the difficulty with disease eradication comes from the demand side of the vaccine market.

[95] Professor Stiglitz 's article was broadly on technological knowledge and intellectual property

Under the Labour government (1997-2010), health literacy was considered a health inequalities issue in England (DH, Department of Health 2008). Fundamentally, on what basis can health literacy be considered a health inequality? Taking a social justice perspective, is it equality based on rights (i.e. access to healthcare), primary goods (i.e., self-respect and freedom of speech) or functioning in health? Perhaps the best fit is to suggest that health literacy is an inequality of opportunity in health. Rosa Dias's (2009) definition, based on Roemer's (2002) model, is that: *"Equality of opportunity in health attains when average health outcomes are identical across types, at fixed levels of effort."* This means that, on average, all those who adopt identical lifestyles should be entitled to experience a similar health status, irrespective of their circumstances.[96] For an empirical analyst, how does one measure inequality of opportunity in health? Equality of health can be formulated by gaps, ratios, shortfalls, or ginis.[97]

As social disparities tend to exist outside of the healthcare sector, they are considered to be distinct from health inequality issues. Because of a clustering of risks to health (e.g. poverty, unemployment, low educational attainment), those with limited literacy are more likely to be living in a neighbourhood under circumstances that are associated with high rates of chronic disease (Schillinger, 2010). Ratzan's (2001) 21st Century Field Model presents a conceptual framework to link health literacy application of primary, secondary, and tertiary medical prevention with determinants of health (i.e., social, physical, and environmental), education, income, and vulnerability or risk factors. Ratzan (2001) concluded that, in order to attain health literacy, policymakers and leaders outside of the health sector must be aware of the critical elements that contribute to health illiteracy such as poverty

[96] Such a situation corresponds to a full nullification of the effect of circumstances—keeping untouched the differences in health outcomes that are caused solely by effort.
[97] The gini coefficient is a measure of the inequality of a distribution [e.g., opportunity], a value of 0 expressing total equality and a value of 1 maximal inequality.

and lack of formal education. In the US, Health Literacy Missouri (HLM) is an example of an organisation that takes a public health approach. They guide healthcare providers in turning their organisation into a less complex healthcare environment for all their patients. [98]

Parker's health literacy framework (2009) allows health literacy to be neatly motivated to policy-makers - If health literacy is to be viewed as a predominate health inequalities or disparities issue, policy-makers would focus on improving the skills or abilities of specific disadvantaged groups. Alternatively, if health literacy were to be viewed as predominately a public health issue, policy-makers would need to focus on lessening the demands of the healthcare system for all citizens. Arguably, Volandes, and Paasche-Orlow (2007) best summarised the ethos that any healthcare system should view health literacy as:

"Instead of assuming literacy and then trying to retrofit care for low literacy patients as some form of speciality service, application of the maximin principle (Rawlsian approach) leads us to the conclusion that the standard of care should be reoriented to the needs of health consumers with limited literacy". [99]

Global organizations such as the World Health Organization (WHO) and the United Nations (UN) are embracing the health literacy perspective and view it as akin to financial literacy (Mayagah and Mitic, 2009)(United Nations, 2010). Furthermore, the US has a National

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[98] HLM is a not-for-profit organization headquartered in St. Louis, Missouri that bringstogether a wide range of healthcare providers, advocates and organisations with individual missions, but a common goal: To help people make good health decisions every day. They also conduct health environment assessments for healthcare providers.
http://www.healthliteracymissouri.org/(accessed: March 20th 2014)

[99] The basic structure is just throughout when the advantages of the more fortunate promote the well-being of the least fortunate, that is, when a decrease in their advantages would make the least fortunate even worse off than they are. Alternatively, *"The basic structure is perfectly just when the prospects of the least fortunate are as great as they can be."* -- Rawls, 1971, p 328

Action Plan on health literacy.[100] In a country like Ireland that does not have a health literacy policy, the question is whether policy-makers should view health literacy as predominately a public health or health inequalities issue? That is to say - Is value for money is best achieved by targeting health literacy interventions as the lower socioeconomic class? An angle to answer that question is whether there is evidence of a strong gradient for those that demand a health literate healthcare system, which is the research question posed in the next section of this thesis.

[100] US Department of Health and Human Services, Office of Disease Prevention and HealthPromotion2010http://www.hsph.harvard.edu/healthliteracy/files/2012/09/national_action_plan_to_improve_health_literacy.pdf (accessed: 17th March 2014) In October 2010, President Obama signed The Plain Writing Act of 2010, which requires that each federal agency use plain English in every document that the agency issues or substantially revises to the general public.

6.4 Health Literacy in Ireland – An Empirical Analysis

If an overarching policy question on health literacy is posed as: Should Irish health policy-makers view health literacy as predominately a public health or a health inequalities issue? Then, the answer to that question will probably depend on whose perspective and what evidence is available. As an empirical analysis that may feed into that debate, the research question that is posed in this section is: What evidence is there that a socioeconomic gradient exists in those that seek/demand a health literate healthcare system? The attempt to answer this specific question involves analysing nationally representative survey data and focusing on the socioeconomic characteristics of respondents in relation to questions about strategies to improve their general health. A variable is constructed that represents a respondent's demand or motivation for a health literate healthcare system. Then, this variable is examined across the socioeconomic gradient. Part of this approach is akin to income-related inequality in health literature which focuses on the variation in health as one moves along the distribution of income (Kakwani et al., 1997)(van Kippersluis et al., 2010).

Data - Survey of Lifestyle, Attitudes and Nutrition (SLAN)

Two cohorts (1998 & 2002) of nationally representative household survey data commonly known as SLAN is used as the data source.[101] This health and lifestyle survey aimed to describe the health-related lifestyle behaviours (i.e. exercise, smoking, drinking, eating habits, etc.) of Irish society. Briefly, SLAN is a cross-sectional survey, using a stratified probability sampling design. A two-stage random sample was drawn based on the adult population in each of the Republic of Ireland's 26 counties and was proportionately distributed according to

[101] An unsuccessful attempt was made to get the 2011 European Union- Health Literacy Survey (EU-HLS) data, which would be a much better source to look at the relationship between health literacy and the healthcare system.

the urban/rural breakdown in each county. The sampling unit within each county was the district electoral divisions (DEDs) and the required number of urban and rural DEDs was ascertained based on census data. Within each DED a random sample of 50 Irish adults aged 18 years and over on the electoral register was generated by a subsidiary company of the national postal system.[102] In 1998, each selected adult was sent a self-administered questionnaire, plus explanatory letters and prepaid reply envelopes, of which 6,539/12,733 (51.3%) were returned. Four years later (2002), a similar survey was conducted and 5,992/11,212 (53%) persons participated. There was remarkable between-survey consistency in many variables enabling the data to be pooled for analysis purposes (Shiely et al., 2010).[103] The reason for pooling was to increase the sample size. The final analytic sample for this analysis was 12,513 as 18 respondents were removed due to incompleteness of basic demographic information.

Demand for a Health Literate Healthcare System Variable:

The demand for a health literate healthcare system variable was derived from two questions from the general health section asked in both the 1998 and 2002 survey. The first question was framed as: "*I think my own health would be better if I had…."* The respondent was given 16 prompted answers and prompted to tick all that apply, including three answers that elicited a demand for a health literate healthcare system - (a) "*Better information about where to go for healthcare*"; (b*) "Easier to read health information"* and (c) "*Better information about how to stay healthy"*. The second question was framed: "*Which of the following do you think prevents people from improving their general health?"* The respondent was given 7 prompted

[102] The sample was generated randomly from the Irish electoral register supplied by Precision Marketing Information (PMI) Ltd., a subsidiary of An Post (The Irish Postal Company)

[103] The 2007 SLAN survey was completely different format and not suitable for this analysis

answers and prompted to tick all that apply Two aspects of the demand for a health literate healthcare system answers were (a) *"Not being able to read and understand information"* and (b) *"Lack of information".* For the empirical analysis, the constructed demand for a health literate healthcare system variable was made binary by giving a respondent a value of 1, if they ticked 1 or more boxes that elicited a demand for a health literate healthcare system and 0 otherwise. [104]

Independent Variables:

The basic conceptual model (Figure 22) reflects the individual characteristics that are likely to motivate a demand for a health literate healthcare system in the SLAN survey. It is probable that respondents would have an array of other unobservable variables (e.g. extent of previous experiences with the healthcare system) that are not captured in the survey. Therefore, the SLAN data was not suitable in establishing the causal factors of the motivation for desiring or demanding a health literate healthcare system but merely the associations.

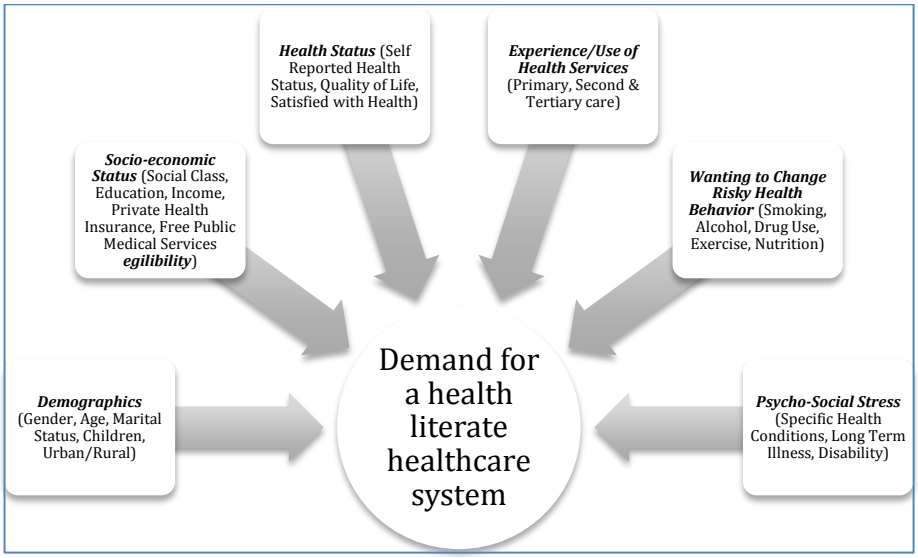

Figure 22: Conceptual model of characteristics that contribute to a respondent's demand for a health literate healthcare system in SLAN

[104] A count model was also examined but the interpretation of the analysis is not as intuitive as a binary model.

Of the socioeconomic variables, the main independent variable in the regression analysis was 'social class group' – this was determined based on the occupation of the principle wage earner in the household and was categorised based on the Irish Census 1996 classification system. Other variables were characterised under the following umbrella terms: *Demographic* - Gender, age group, marital status, living arrangements, location. *Socioeconomic status* - Social class, education, income (2002 only), private health insurance (2002 only) eligibility to free public medical services with a medical card is a robust proxy of disadvantage as is means-tested (Kelleher, 2007).[105] *Risk behaviour and attitude* - Smoking, alcohol consumption, ever drug use, exercise and nutrition. *Health status or psychosocial stress* - Specific health conditions, long-term illnesses and disability. (See Table 25 for full listings).

Table 25: SLAN variables and description

Variable	Description
Dependent Variable	
Demand for a health literate healthcare system	The first question was framed: I think my own health would be better if I had…. responses included: (a) "*Better information about where to go for healthcare*"; (b*) "Easier to read health information"* and (c) "*Better information about how to stay healthy"*. The second question was framed: "*Which of the following do you think prevents people from improving their general health?"* Responses included: (a) *"Not being able to read and understand information"* and (b) *"Lack of information".* 1=if respondent ticked any of the responses, 0 otherwise
Main independent variable	
Social class grouping	

[105] In Ireland, GP and other medical services are provided free-of-charge to all below a set level of income. This entitlement is generally referred to as possessing the general medical services (GMS) card. Eligibility at the time of the surveys was assessed on a case-by-case basis at regional health board level and factors like age, income and post-retirement means were taken into account. In 2003, it was reported that approximately a third of the population were entitled to the benefits of the scheme (Kelleher et al., 2003).

Social class 5 or 6	1=Semi-skilled, unskilled labour, 0 otherwise
Social class 3 or 4	1=Non-manual, skilled manual operator, otherwise
Social class 1 or 2	1=Professional, managerial and technical, 0 otherwise
Explanatory variables	
Demographics	
Gender	1=Female, 0 = Male
Age 18-34	1=Aged between 18-34 years, 0 otherwise
Age 35-54	1=Aged between 35-54 years, 0 otherwise
Age 55+	1=Aged between 55 years or older, 0 otherwise
Married	1=Married, 0 otherwise
Previously married	1=Previously married, 0 otherwise
Cohabiting	1=Cohabiting, 0 otherwise
Single	1=Single, 0 =otherwise
DED type (Location)	1=Urban, 0=Rural
Living arrangements	1=Living with others, 0 = Alone
Socioeconomic status	
Primary	1=Primary education or less, 0 otherwise
Secondary	1=Secondary education, 0 otherwise
Tertiary	1=Tertiary education, 0 otherwise
Employed	1=Employed, 0 otherwise
Retired	1=Retired, 0 otherwise
Student	1=Student, 0 otherwise
Unemployed	1=Unemployed, 0 otherwise
Medical Card[106]	1=Yes, 0 = No
Private health insurance (2002 only)	1=Yes, 0 = No
Household tenure	1=Owned with mortgage or outright, 0 = Rented
Risk behaviour	
Smoking	1=Smoker, 0 = non-smoker
Physical activity	1=Regular exercise, 0=No exercise
Alcohol use	1=Exceed limits, 0 = Within limits
Drug use	1=Has tried, 0= Never Tried
Fried food	1=Eaten fried food >1 per week, 0 Eaten fried food <1 per week
Health or psychosocial stress	
Self reported health	

[106] Entitlement to a medical card for over-70s was put in place in 2001 and this may affect the reliability of this variable as a proxy for disadvantage for the 2002 dataset. According to the Central Statistics Office (CSO), the proportion of those over-70 with both medical card and private health insurance in 2001 was 10%. In 2001, 4% of over-70s had neither a GMS card nor private health insurance.
Source:
http://www.cso.ie/en/media/csoie/releasespublications/documents/labourmarket/2010/healthstatusq32010.pdf (Accessed: 30th June 2013)

Excellent	1=Excellent, 0 otherwise
Very good	1=Very good, 0 otherwise
Good	1=Good, 0 otherwise
Fair	1=Fair, 0 otherwise
Poor	1=Poor, 0 otherwise
Self reported quality of life	
Excellent	1=Excellent, 0 otherwise
Very good	1=Very good, 0 otherwise
Good	1=Good, 0 otherwise
Fair	1=Fair, 0 otherwise
Poor	1=Poor, 0 otherwise
Satisfaction with health	
Very satisfied	1=Very satisfied, 0 otherwise
Satisfied	1=Satisfied, 0 otherwise
Neither satisfied nor dissatisfied	1=Neither satisfied nor satisfied, 0 otherwise
Dissatisfied	1=Dissatisfied, 0 otherwise
Very dissatisfied	1=Very dissatisfied, 0 otherwise
Specific health conditions	1=At least one specific condition 0 = No specific condition
Long-term illnesses/disabilities	1=Yes, 0=No

Methods

A brief descriptive analysis of the demand for a health literate healthcare system variable is followed by a bivariate analysis between the binary demand for a health literate healthcare system variable and the explanatory variables. Then, by adding independent variables in a stepwise manner, various multivariate logistic regressions were run. Starting with demographic variables followed by socioeconomic status, risk behaviour and attitude, health status and psychosocial stress variables.

The motivation for construction of a concentration curve is that it is a novel approach to graphically illustrate if inequalities exist in the demand for a health literate healthcare system by equivalence self-

reported income variable.[107] The concentration curve akin to those used to show health inequalities was constructed (Kakwani et al., 1997)(Wagstaff et al., 1991). A concentration curve is a graphical way to illustrate whether the variable being analysed has a pro-rich or pro-poor bias. Individuals are ranked from the poorest to richest and their cumulative share of demand for a health literate healthcare system variable is plotted. This strengthens the analysis beyond using odds ratios to show differences between groups.

A concentration curve plots shares of the demand variable against quintiles of the income variable. If everyone, irrespective of his or her income, has exactly the same value of the motivation variable, the concentration curve will be a 45-degree line. If the demand variable takes higher values among poorer people, the concentration curve will lie above the line of equality and have a pro-poor bias. If the converse were observed, the concentration curve would give a pro-rich bias. Also, a concentration index is a measure of the magnitude of the inequality (O'Donnell et al., 2008). The concentration index is defined as twice the area between the concentration curve and the line of equality. So, in the case where there is no income-related inequality, the concentration index is zero. The concentration index is a summary measure and should be examined in conjunction with the concentration curve. Formally, the Concentration index (CI) can be calculated as:

$$CI = \frac{2}{N\mu}\sum_{i=1}^{n} h_i r_i - 1 - \frac{1}{N}\,, \qquad h, \in \{0,1\}$$

Where h_i denotes the dependent variable of interest (e.g. demand for health literate healthcare system), μ represents its mean and r_i denotes

[107] In the 2002 survey, the following question was asked: *"What is your household's total net income per week, i.e. the take-home family weekly income from all sources (include social benefits, etc)?"* There were 15 response options available from lowest 'less than €65' to highest '€1,900 or more'. The income variable was transformed into an equivalence income variable based on number of adults and children living in the household and only the 2002 SLAN dataset contained this variable.

the fractional rank of each individual along the equivalised income distribution. Here $i = 1$ for the individual at the bottom of the income distribution (the poorest in the sample) and $i = N$ for the individual at the top of the distribution (the richest in the sample). The sign of the concentration index indicates the direction of any relationship between the health variable and position in the living standards distribution, and its magnitude reflects both the strength of the relationship and the degree of variability in the health variable (O'Donnell et al., 2008). [108]

As the dependent variable in this chapter is binary (e.g. whether respondent has a demand for a health literate healthcare system), a normalisation is required so that the concentration index is bounded in the range -1 to 1. Two different approaches are available for this, namely Wagstaff and Erreygers normalisations (Walsh and Cullinan, 2014) - Wagstaff correction is given as $CI_n = \frac{CI}{1-\mu}$ and has been used in assessing childhood vaccinations (Wagstaff, 2005). The choice of CI index is dependent on the measurement scale (Erreygers and Van Ourti, 2011) and debate is ongoing in the literature about which is best.

All analyses were conducted in Stata 11.2 software (StataCorp, College Station, Texas, USA) with the glcurve program used to construct the concentration curves and indices.

Results

The percentage of the combined pooled sample that expressed a demand for a health literate healthcare system was 45.7% (5,718/12,513). Of those, 3,228 respondents (25.8%) ticked one attribute, 1,528 (12.2%) ticked 2 attributes, 602 (4.8%) ticked 3 attributes, 257 (2.1%) ticked 4 attributes and 103 (0.8%) ticked all 5

[108] Koolman and van Doorslaer (2004) have shown that multiplying the value of the concentration index by 75 gives percentage of the health variable that would need to be (linearly) redistributed from the richer half to the poorer half of the population (in the case that health inequality favours the rich) to arrive at a distribution with an index value of zero.

attributes. Almost half of the surveys' respondents felt that at least one attribute of a health literate healthcare system would improve general health.

Bivariate analysis

The bivariate associations between the demand for a health literate healthcare system and the explanatory variables are summarised in Table 26. Those with poorer health or lower psychosocial stress variables were statistically significant (p-value = 0.05) associated with a demand for a health literate healthcare system. Older (55yrs+), females, from social class of unskilled/semi-skilled labour, with just primary education, eligible for medical card, living in an urban area and unemployed were proportionally more likely to report a demand for a health literate healthcare system.

Table 26: Bivariate associations between the demand for a health literate healthcare system and variables

Variable	Category	Count[#]	% Respondents demand ≥1 attribute of health literate healthcare system	Chi Square
Gender	Female	6,892	47.5	11.26 *
	Male	5,379	44.4	
Age Group	18-34	3,893	43.6	26.03*
	35-54	5,028	45.7	
	55+	3,317	49.6	
Marital Status	Single	3,907	46.1	4.78
	Married	6,425	45.6	
	Previously	1,384	48.7	
	married	503	43.4	
	Cohabiting			
DED Type	Urban	5,340	47.3	6.87*
	Rural	6,132	44.9	
Living	Alone	1,795	48.1	3.30
arrangements	With others	10,593	45.8	
Social class	SC 1/2	4,091	44.3	10.76*
	SC 3/4	3,516	45.1	
	SC 5/6	1,737	48.9	
Education	Primary	2,190	51.7	34.76*
	Secondary	5,459	45.0	
	Tertiary	3,644	44.2	
Employment	Unemployed,	638	50.2	25.64*
	Employed	6,359	44.0	
	Retired/Student	4,452	48.5	
Medical card	Not Eligible	8,360	44.3	37.91*
status	Eligible	3,416	50.5	
Private Health	Yes	3,148	46.5	2.92

Insurance (2002 data)	No	2,461	48.8	
Household tenure	Rented	2,415	49.4	12.21*
	Owned with mortgage/outright	9,610	45.5	
Smoking	Non-smoker	8,723	46.5	1.81
	Smoker	3,455	45.1	
Physical Activity	No Exercise	3,108	46.3	0.08
	Exercise	9,049	46.1	
Alcohol use	Within limits	4,873	45.7	0.07
	Exceed limits	1,500	43.1	
Drug use	No	10,100	46.1	0.19
	Yes	1,802	46.7	
Fried food	<1/Week	6,142	46.9	0.07
	>1/Week	5,850	45.3	
Self-reported Health	Poor	247	57.5	31.71*
	Fair	1,447	50.6	
	Good	4,281	45.7	
	V. good	4,396	45.4	
	Excellent	1,823	43.2	
Quality of Life	V. Poor	142	59.9	34.87*
	Poor	289	54.3	
	Neither	1,433	49.8	
	Good	6,638	46.2	
	V. Good	3,563	43.7	
Satisfaction with health	V. Dissatisfied	220	57.7	26.14*
	Dissatisfied	1,101	48.0	
	Neither	2,036	48.1	
	Satisfied	6,598	46.0	
	V. Satisfied	2,088	42.8	
Specific Health conditions	None	8,008	44.6	22.71*
	At least 1	4,329	49.1	
Long term illness/ disabilities	No	10,104	45.1	39.06*
	Yes	1,586	53.5	
Healthcare use	No	833	40.5	11.60*
	Yes	11,459	46.6	

* P value<0.05; ns: . DED – District Electoral Division. SC 1/2 – professional, managerial and technical; SC 3/4 – non-manual, skilled manual SC 5/6 – semi-skilled and unskilled manual; #Count based on full case analysis.

Logistic Regression

Odds ratios from various multivariate logistic regression models are given in Table 27. The inclusive (all potential explanatory variables) model 4 shows that older respondents (55+yrs) or those who have ever used drugs were more likely to demand a health literate healthcare system. The SES variables, such as social class and having a medical card, were not statistically significant in this model.

Table 27: Multivariate logistic regression of the demand for a health literate healthcare system

Demand for a health literate healthcare system	Model 1: Demographics	Model 2: Socioeconomic status	Model 3: Risk behaviour/ Health/ Psychosocial stress	Model 4: All explanatory variables
Gender				
Male	REF			REF
Female	1.14[1.05 – 1.23]*			1.13[0.98-1.31]
Age Group				
18 – 34years	REF			REF
35 -54 years	1.14[1.03-1.26]*			1.12[0.94 – 1.35]
55+ years	1.34[1.18-1.51]*			1.55 [1.15– 2.08]*
Marital status				
Single	REF			REF
Married	0.92 [0.83-1.02]			1.00(0.82 -1.21)
Previously married	0.92[0.79 -1.06]			0.70(0.50 -0.97)*
Cohabiting	0.97[0.80-1.18]			0.86(0.63-1.15)
ED type	REF			REF
Rural	1.10 [1.02-1.19]*			1.11 [0.98 -1.27]
Urban				
Living arrangements				
Alone	REF			
With others	0.94 [0.86-1.04]			0.91 [0.75 -1.10]
Social Class groups				
SC 5/6 (Semi-skilled/unskilled labour)		REF		REF
SC 3/4 (Non-manual/ skilled manual operator)		0.91[.80-1.05]		0.88[0.71 – 1.07]
SC 1/2 (Professional, managerial + technical)		0.95 [0.83 -1.09]		0.82[0.66 – 1.01]

Education			
None/primary	REF		REF
Secondary	0.79 [0.68 -0.92]*		0.93 [0.70 – 1.22]
Tertiary	0.80 [0.68-0.94]*		0.93[0.68 – 1.27]
Employment			
Unemployed	REF		REF
Employed	0.85[0.68-1.07]		0.81 [0.59 – 1.12]
Retired/Student	0.95[0.75-1.18]		0.77 [0.55 – 1.08]
Medical card			
No	REF		REF
Yes	1.08 [0.96 -1.23]		0.92 [0.75 – 1.13]
Household tenure			
Rented	REF		REF
Owned with mortgage /outright	0.92[0.82-1.04]		0.91 [0.76 – 1.08]
Smoking			
Non-smoker		REF	REF
Smoker		0.88 [0.78 – 0.99]*	0.94 (0.81 – 1.10)
Physical Activity			
No exercise		REF	REF
Exercise		1.09 [0.94 -1.27]	1.02 (0.85 -1.25)
Alcohol use			
Within limits		REF	REF
Exceed Limits		0.90 [0.79-1.02]	0.93 (0.79 – 1.09)
Drug use			
No		REF	REF
Yes		1.10 [0.97 -1.27]	1.19 (1.01 – 1.41)*
Fried Food			
<1/week		REF	REF
>1 /week		0.89[0.80-0.99]*	0.95 (0.82 -1.09)

Self Reported Health				
Poor			REF	REF
Fair			1,17[0.62 -2.21]	0.52 [0.29 -1.29]
Good			1.35 [0.72 -2.57]	0.58[0.23– 1.48]
Very Good			1.44[0.75 – 2.75]	0.66 [0.26 – 1.68]
Excellent			1.33 [0.69 -2.56]	0.62 [0.25 -1.61]
Quality Of Life				
Very Poor			REF	REF
Poor			0.66[0.31 -1.41]	0.57 [0.22 – 1.49]
Neither poor or good			0.47[0.23 -0.84]*	0.47 [0.21 – 1.03]
Good			0.37[0.20 -0.69]*	0.45 [0.21 – 0.95]*
Very good			0.33[0.18-0.61]*	0.39 [0.19 – 0.81]**
Satisfaction with health				
Very dissatisfied			REF	REF
Dissatisfied			0.54[0.31 -0.95]*	0.70 [0.34 – 1.42]
Neither satisfied nor dissatisfied			0.61[0.35-1.07]	0.81 [0.40 – 1.64]
Satisfied				
Very satisfied			0.65[0.38-1.14]	0.87 [0.43 - 1.75]
			0.64[0.37 -1.14]	0.79 [0.38 – 1.62]
Specific Health conditions				
No Specific condition			REF	REF
At least 1 specific condition			1.07 [0.95 -1.22]	1.02[0.87 – 1.20]
Long term illnesses/disabilities				
No				
Yes			REF	REF
			1.35 [1.10-1.67]*	1.14 [0.87 -1.50]
N	10,978	7,888	5,586	3,695
BIC	15180	10909	7800	5324
Pseudo-R^2	0.0035	0.0032	0.0081	0.0113

* P>0.05 ** P > 0.01

The concentration curve (Figure 23) showed that the motivation for a health literate healthcare system had a very slight pro-poor bias and that the concentration index (-0.016) was very close to equality (zero).[109] This suggests that the demand for a health literate healthcare system was seen across the SES of this nationally representative sample.

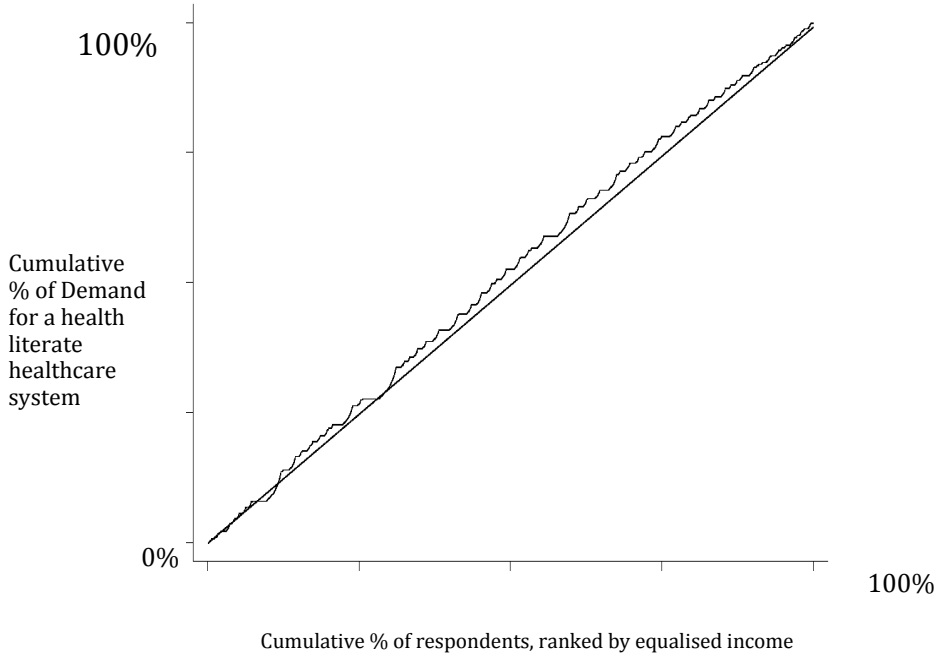

Figure 23: Desire for a health literate healthcare system concentration curve using SLAN 2002

Discussion of SLAN Analysis

To the best of my knowledge, this empirical analysis is the first time that a researcher has examined the demands/complexities side of the health literacy framework using individual-level survey data. Most of the research in health literacy is on the skills of respondents. This analysis assesses whether there is a demand for a health literate healthcare system. The US health literacy community have had great success in focusing on reducing the demands of the American

[109] Wagstaff normailise concentration index is -0.029 and Erreygers = -0.055. The percentage of the demand for health literate healthcare system variable that would need to be redistributed from the richer half to the poorer half of the population to arrive at a distribution with an index of zero is about 1-4% depending on the value of concentration index used.

healthcare systems. The constructive demand for a health literate healthcare system is inferred from responses available in a survey. [110] Descriptive analysis of this variable indicates that nearly half of the SLAN respondents express a demand for attributes of a health literate healthcare system. This is a significant result in of itself. It suggests that there is a demand from the public to have an easier-to-understand healthcare system in Ireland. The principal research question asked whether those respondents that expressed a demand for a health literate healthcare system came from a certain sector of Irish society? Based on logistic regression and inequalities analysis, it appears that the respondents that demand a health literate healthcare system in Ireland come from right across the socioeconomic gradient.

The bivariate association of explanatory variables and the demand for a health literate healthcare system indicate those from the lower socioeconomic gradient have a higher demand for a healthcare system. However, the preferred multivariable logistic regression model (Model 4) refutes this association albeit with caveat there are a large number of missing values, which limits generalizability and the pseudo-R^2 is very small (0.0113). The next piece of analysis looks graphically at inequalities using a concentration curve. No discernable difference can be seen from the line of inequality. The concentration index was also not significantly different from zero (CI =-0.016), therefore there was no benefit in decomposing the socioeconomic inequality – similar to others that show significant socioeconomic inequalities in childhood obesity (Walsh and Cullinan, 2014) and vaccination (Doherty et al., 2014).

[110] IOM's Health Literacy Roundtable brings together leaders from academia, industry, government, foundations and associations, and representatives of patient and consumer interests who work to improve health literacy. To achieve its mission, the Roundtable discusses challenges facing health literacy practice and research, and identifies approaches to promote health literacy through mechanisms and partnerships in both the public and private sectors.
http://www.iom.edu/Activities/PublicHealth/HealthLiteracy.aspx (accessed: 17th April 2014)

The SLAN data has a number of important limitations in answering the policy question. The data is now 12-16 years old and would not capture the impact that immigration has had on public healthcare services.[111] It is likely that an important component of being a health literate healthcare system (i.e. to deliver culturally and linguistically appropriate services) is not substantially addressed by the Irish healthcare system. Ireland has also experienced a 'boom-to-bust' economic cycle, which has resulted in close to 50% of the population now having a medical card, a legacy of an entitlement given to the over-70s in the boom era and due to financial troubles in the bust.[112] The 'social class' variable was a very crude measure of social standing; hence other variables such as education, employment, GMS card status and household tenure were also analysed in the regression analyses. The self-reported household income was only reported in 2002 allowing construction of a concentration curve for that time-period only.

Health Literacy and Policy

From the demands/complexities side of the health literacy framework, the SLAN analyses suggested that health literacy's role in health policy should be predominately conceptualised as a public health issue. This is because the demand for a health literate healthcare system is seen across the socioeconomic gradient. The Irish results of the 2011 European Union Health Literacy Survey (EU-HLS) showed a significant positive association between those with higher health literacy scores and higher social class, education level and self-reported income in

[111] The 2006 census indicated that 420,000 of the Irish population are foreign-born nationals domiciled in Ireland. Source: http://www.cso.ie/en/releasesandpublications/population/archive/publicationarchive2006/census2006-non-irishnationalslivinginireland/ (accessed: 17th April 2014)

[112] Irish Examiner. Almost half of population holds medical card. Available from: http://www.irishexaminer.com/breakingnews/ireland/almost-half-of-population-holds-medical-card-584564.html (accessed: 12th February 2014)

Ireland (Doyle et al., 2012).[113] This would be an ideal dataset to construct a concentration curve and decompose a concentration index (if appropriate). The report authors did make the concluding point that: *"Although health literacy is undoubtedly related to markers of social gradient such as income and education, these findings suggest that a direct linear relationship should not be assumed, those with higher incomes and more education are still at risk of low health literacy"* (Doyle et al., 2012).

Irish policy-makers could draw inspiration from the IOM (2012) discussion paper - Ten Attributes of Health Literate Health Care Organizations, which sets out how healthcare systems can make it easier for people to navigate, understand, and use information and services to take care of their health. This approach would also apply to specific aspects of the healthcare system like cancer services. In thinking about the subject matter of this thesis, HPV-related HNC, the complexity of cancer-related information about prevention, early detection, treatment, recovery, and end of life challenges should be kept to a minimal. To do so effectively, health literacy principles ought to be embedded in cancer communication in order to reduce the demands on citizens not familiar with medical jargon.

[113] EU-HLS developed an instrument to measure health literacy in Europe. This model has 4 main competencies necessary to be considered health literate. These competencies relate to access, understanding, appraisal and application. The Newest Vital Sign, a validated measure of functional health literacy, was also used as an instrument to assess respondents' skills/abilities in the EU-HLS (Weiss et al., 2005).

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Chapter 7: Summary of Dissertation Findings and Policy Recommendations for HPV-related Head and Neck Cancer

As the nature of cancer continually evolves, so too does the scientific community's understanding of what causes cancer and how best to prevent cancers and treat patients. From discovery some fifteen years ago, HPV-related HNC became one of the biggest public health stories of 2013. In the US, Jemel et al. (2013) influential Annual Report on the Status of Cancer was dedicated to the virus and the role that HPV vaccination could have in arresting or slowing this current epidemic. It was Michael Douglas's public discussion, however, that really propelled the topic into the public domain in the US.

In Ireland, HPV-related HNC had not been discussed in any great detail in medical and social science literatures. Despite this dearth of discussion, the HRB-sponsored *Knowledge Exchange and Dissemination Scheme Symposium* on May 17th 2013 in Galway has brought the issue to national and international prominence, which has helped the outputs of this thesis to have some influence in policy circles.

Chapter 2 discussed the pertinent issues that the reader who is unfamiliar with HPV and HNC needed to know, such as risk factors, epidemiology, detection, treatment and public health options. This prefatory chapter argued that a range of factors from various disciplines converge on the assertion that HPV-related HNC also has *a distinct economic profile*. Although the vast majority of oral HPV infections are cleared, a weaken immune system seems to aid the virus in remaining dormant in the oropharynx region, where over many years it contributes to cells turning cancerous. Patients who have HPV-related HNC are on average younger males, more likely to have a higher socioeconomic status, higher educational attainment and more likely to have more sexual partners over the course of their lifetimes than non-HPV related HNCs (Gillison et al., 2008)(Benard et al., 2008).

Those sociodemographic variables are likely to be important factors in seeking and utilising healthcare services in the US. In essence, this cancer could potentially affect all sexually active humans given the ubiquitous nature of the virus and be a major strain on cancer services in the near future.

The detection of HPV in HNC has recently emerged as a powerful biomarker. Patients with a HPV-positive test result have a lower risk of tumor progression and death than patients with HPV-negative tumours independent of treatment (Gillison et al., 2000)(Ang et al., 2010)(Fakhry et al., 2008). With a greater likelihood of survival and a longer life span over which long-term complications (especially swallowing difficulties) arising from treatment may manifest themselves, the choice of optimal treatment modality becomes even more imperative for these patients and for those with financial responsibility for the cost of their care (Li and Richmon, 2012).

Evidence from France has shown that the economic burden of HPV-related HNC is fast approaching that of cervical cancer, prompting the need to explore new prevention strategies (Borget et al., 2011). The consensus has been that achieving high-rates of vaccinations among girls will offer 'herd protection' to boys and would be more cost-effective strategy (Kim and Goldie, 2009). This strategy neglects the fact that geographical borders neither restrict sexual networks nor do they protect the MSM population from the virus. Another viewpoint is that vaccinating girls only can potentially exacerbate the problem of health and sexual health literacy among boys.

One of the biggest limitations with CEA models of gender-neutral HPV vaccinations is the poor quality of data regarding the cost-per-case of oropharyngeal cancer and the underestimation of the percentage of cases caused by HPV-16/18.

Chapter 3 undertook a literature review of the known burden of HNC in the US incorporating a focus on HPV. Epidemiological metrics

highlight the epidemic nature, significance (with respect to other HPV-related cancers) and the longer survivorship phase of these patients. HPV-positive cancers in the oropharynx will surpass cervical cancer in incident cases by 2020 in the US if current trends persist (Chaturvedi et al., 2011). This looming public health impact of HPV is a call-to-action for policy-makers. With respect to the economic burden, the review identified seven studies that reported estimates of direct medical costs and productivity losses of HPV-related HNC in the US.

Hu and Goldie's (2008) estimate that the total lifetime costs for new cases of HPV-related HNC in 2003 was $38.1m (Range: $17.7 to $54.1m) was based on a HPV prevalence of 10.7%. This estimate is somewhat lower than the more recent epidemiological estimates by the CDC of 72%. The most cited cost-per-case of HNC by Lang et al. (2004) looked at Medicare patients only from 1991-1993 and the total mean Medicare 'payments' was $48,857 (1998 USD). However, as noted in the MEPS study on HNC, payments, charges and expenditures represent different 'cost' measures. The Lang et al. (2004) estimate is therefore likely to be an underestimation of the payment for HNC treatment in the US in 2014. The true economic 'cost' estimate of a HNC case (HPV-related or not) can be derived from cost-to-charge ratios. As the era of personalised medicine dawns, patients are likely to undergo a combination of surgery, radiation and chemotherapy, depending on a number of clinical factors. Subsequently, an accurate cost-of-care estimate for HNC case (HPV-related or not) is likely to be a function of individual characteristics (e.g. age); treatment protocols based on smoking and HPV status; and payer reimbursement rates. Interestingly, the importance of testing for HPV may also be cost-saving; if, as demonstrated in an Australian study that only 2 of 126 (1.6%) of HPV-positive oropharyngeal patients were suitable for cetuximab ($10,000+ per treatment cycle), then older, cheaper chemotherapy agents (e.g. cisplatin) may be more suitable for HPV-positive oropharyngeal cancers (Young et al., 2011). As the suitability

for cetuximab is based on the molecular biology of the cancer, it follows that the chemotherapy treatment responses will not be the same.

The absence of guidelines establishing reliable methods for estimating the economic burden gives rise to huge variation in the derived estimates, and the biggest factor is determining what to include in a COI study. Does the COI include productivity losses and if so, how are they calculated? Human capital or friction costs? Another methodological factor is whether the study captures incidence or prevalence direct medical cost estimates? The data source, nature and quality of the information captured (e.g. self reported medical expenditures) and the sample captured are critical details to the validity of such estimates. For instance, Ekwueme et al. (2008) estimated the societal mortality-related burden (in terms of YPLL and productivity costs) in the United States in 2003. This study is probably the most informative for public policy-making and puts an annual figure of $1.37bn on the total mortality costs of HPV-related HNC using a human capital approach.

The main observations regarding the studies reviewed in chapter three are how heterogeneous HNC patients are. The second observation related to the subjective nature of the methods used in economic burden studies. The third observation from the review noted that the disease-specific estimate does raise methodological concerns - specifically the 'adding-up' constraint, which is when it is not entirely clear to the analyst what costs are associated with which disease, and how to ensure that all medical spending is allocated to one and only one disease. A major improvement in characterising the epidemiological and economic burden of HPV-related HNC in the US would be to recognise that HPV-related HNC cancer is distinct from other types of HNC. Without ICD codes indicating to an analyst that a patient has HPV-positive HNC, the *de facto* situation will be the

reference to HPV-related HNC sites adjusted by percentage that are HPV-positive from other studies.

The most measurable part of any economic burden or COI study is identifying the direct medical expenditures (costs) attributable to the disease. **Chapter 4** was devoted to estimating the direct medical expenditures component of a COI study for HNC. The analytic sample was constructed from the publicly available MEPS database. To have enough observations to make nationally representative estimates required pooling 6 years of data (2003 to 2008). To link all the various files (e.g. condition-event files) for 6 years was time-consuming and was likely to deter other analysts. It is, however, useful to policy-makers to establish where the economic burden falls.

The analysis of the direct medical expenditures was informed by a review of the COI methodology by Akobundu et al. (2006). They identified four analytical approaches – sum all medical costs, sum all disease-specific medical costs, matching and regression. A literature review to identify the most popular approaches taken by other MEPS analysts and then deployed each to estimate the effect of having a history of HNC on medical expenditures was undertaken. The nuances of this study are that the estimates reflect the 'treated prevalence' of HNC and are based on 'person years' and that the pooled data gives the 'average annual' estimate. The total expenditure estimate approach (as expected) gave the biggest national estimate at $3.18bn for the sum all medical expenditures approach. The sum all-disease-specific costs gave a lower national estimate of $1.41bn. Ambulatory visits which consist of outpatient and office-based medical provider made up the vast majority of disease-specific events (87.6%), which were mainly paid for by private health insurance (41%) and Medicare (35%).

The more appropriate estimates of the direct medical expenditures of HNC require a comparison group. The incremental expenditure estimate of HNC was $7,251, using a matching approach (GMATCH).

This matching approach is likely to be a cruder estimate than the more sophisticated propensity score matching approaches available in R and Stata. This matching approach may become more popular with health economists in the future. The regression approaches estimated the incremental expenditure to be $5,069 (±3,614) using a GLM log link with Poisson distribution and $2,591 (±1,142) using an EEE model. The EEE has been found to be a reliable estimator using MEPS of total healthcare expenditures (Hill and Miller, 2010). The tighter confidence interval around the EEE also makes the estimate more certain. The EEE approach did however suggest that a square root link transformation along with a Poisson distribution would be the preferred GLM approach for this data. The econometric issues that arose from the analyses were also discussed, which highlighted the importance of running model specification tests such as the Pregibon's link test and Pearson test (related to the Hosmer and Lemeshow test). The Modified Park test should also be run to identify the adequacy of the variance function. Given the debate on identifying the best approach, it is increasingly more common for analysts to compare model performance using goodness-of-fit (e.g. R^2) measures from an auxiliary regression of actual costs on the predicted values on the raw cost scale, as well as the related measure of root-mean-squared error (RSME) and the mean absolute prediction error (MAPE) (Jones et al., 2013).

While it is accepted that policy-makers are not the only audience for such studies, the value of a consensus on methods seems evident. In the absence of this, the *caveat emptor* will increasingly ring hollow and the value of economic burden/COI studies will be increasingly called into question. In the empirical analysis, four approaches and an array of incremental methods, some more robust than others, can portray the direct medical expenditure burden. The key findings are that estimates vary substantially depending on the approach used. The incremental methods are a far more realistic model of the burden but are open to analyst manipulation and may lack clarity about what the

best model may be. For a low incidence disease, the MEPS dataset allows for an 'average annual' based on 'person years' estimate of the 'treated prevalence'. The NCI use a phase-of-care incident-based method to generate their estimates. Therefore, my estimates should not be compared with those of the NCI, who are also working off more accurate data and larger samples. There is also a 'burden' in terms of understanding and using these estimates intelligently, which is why reporting the four approaches may give policy-makers some transparency and clarify on the figures presented by analysts. Guidance is therefore needed on how to estimate and report these estimates especially given the appetite in the media and the incentives for special interest groups to pick methods, which yield big numbers.

One of the issues of HPV-related HNC is the substantial and prolonged after-care these patients receive. In **Chapter 5** the healthcare utilisation of the cancer survivorship phase was examined using Irish data. Given the improvement in survival rates in HPV-related HNC and cancer in general, it is perhaps unsurprising that many view cancer as a 'new' chronic condition. The TILDA dataset did not contain enough respondents with HNC to allow meaningful analysis of them as a specific sub-group of cancer patients. It was therefore decided to examine a broader range of survivors. While issues of survivorship are more likely to arise with respect to HPV-related HNC, an examination of care levels and mix after diagnosis among all cancer patients may nevertheless help shed light on how care levels or patterns change as the survivorship phase lengthens. The literature review identified that time since cancer diagnosis and type of cancer are important considerations in any analysis of cancer survivors. The role of the healthcare system is also important and a 'whole system' approach is advocated (Treanor and Donnelly, 2012)

The analyses used in this chapter compared the healthcare utilisation of cancer survivors to those without healthcare across a range of healthcare services (GP, outpatient office visits, daycase, inpatient

admission, emergency room and public health services). Goodness-of-fit criteria and economic theory lead to the use of a hurdle count model to show the nuances in healthcare utilisation of cancer survivors. Those that were within two years of cancer diagnosis had a statistically significant higher probability of using hospital-based services compared to respondents without a history of cancer. The strength of that association dissipated in respondents with a longer history of cancer. However, even a respondent with a cancer diagnosis 11+ years ago has a significant higher probability (~96%) of having an outpatient office visit than someone without a history of cancer. Respondents with a history of cancer also had a higher number of GP and outpatient visits, conditional on their participation in using the healthcare system.

A series of bivariate probit models were run to assess what the level of care was in the presence of suspected unobserved heterogeneity between care models at primary and secondary levels. The positive and statistically significant correlation between the error terms in the estimated equations indicated that there was unobserved heterogeneity present in the estimated equations between GP and hospital services. This unobserved heterogeneity may be related to patient anxiety about their health or they may have a preference for or gain a higher expected utility from visiting both GP and specialists. The TILDA analysis suggested that respondents with a longer history of cancer have a higher probability of outpatient office visits; it's plausible to consider that supply-side factors are also at play. The count models are supported by the bivariate in respect of the level of service use - the correlation in errors suggests that unobserved heterogeneity is present and that the levels varies between services - links with outpatient office visits are much stronger than other services. This may point to a greater gatekeeping role by GPs and merits further investigation. As the demands of cancer services are ever increasing, the transition of survivorship care from secondary to

primary, which is similar to Dutch and British models of care, should be reviewed in Ireland.

The third major empirical work in this thesis is on the theme of cancer communication and presented in **Chapter 6.** The evidence suggested that the awareness of HPV as a carcinogenic among the general public in developed countries is poor. This lack of awareness is likely to have ramifications for uptake of HPV vaccination in boys (should that prove to be a cost-effective strategy). The argument made in chapter six is that the fundamental concept underpinning any good cancer communication strategy is health literacy - a field of research that has been instrumental in shaping healthcare reform in America.

Health literacy aligns the skills or abilities of individuals with the demands and complexity of the healthcare system (Parker, 2009). The empirical analysis using the SLAN survey data has the intention of ascertaining whether or not the demand for a health literate healthcare system is seen across the socioeconomic gradient in Ireland. The complementary policy-related question is whether health literacy should be viewed predominately as a public health or health inequalities issue? Despite major limitations with the data, the various analyses suggest that the demand for a health literate healthcare system is seen across the socioeconomic gradient. Therefore, I hold the view that Ireland should take a predominately public health approach to health literacy and specifically cancer communication especially regarding HPV-related cancers.

Implications for future research

Within each theme, there are implications for future research. In characterising the direct medical expenditure component of a COI study, it is strongly advised that analysts consider a variety of approaches. If the research question involves estimating the incremental expenditure, given a data set with plenty of cases, perhaps a combination of matching and regression would be the best approach.

There is scope to experiment with matching and regression techniques as more sophisticated methods become available for analysts to use. Reporting more than one approach gives a plausible range for the direct medical expenditures, which gives stakeholders upper and lower bounds decreasing uncertainty. However, for this to become standard practice with the MEPS data set, it would require AHRQ to issue guidelines to encourage analysts to report more than one approach.

The analysis of healthcare utilisation of cancer survivors is more nuanced than just having a single variable representing whether a patient has had cancer. Time since diagnosis and type of cancer play a role in explaining variation in use by respondents. However, a data set like TILDA is a great resource for hypothesis generating but for many research questions regarding the follow-up care of cancer survivors, it would be imperative that qualitative research is conducted to confirm or refute the results of the econometric analysis.

It would be great to see future research in the analysis of health literacy on the demands placed on individuals by the healthcare system. However, many health surveys do not ask these types of questions for analysts to analysis. Therefore, future research based on data about health literacy should use concentration curves along with regression analysis to measure any inequality between different social classes.

Implications for public health policy

The policy recommendations for HPV-related HNC in developed countries are set out in Table 28. Proposed multidisciplinary initiatives cover epidemiology, pathology, clinical management, health economics and public health.

Table 28: Proposed multi-disciplinary policy initiatives

Discipline	Achievable Policy Initiatives
Epidemiology	• Retrospective analysis of sample tissue for HPV in associated HNC sites • Oral HPV prevalence studies
Pathology	• Routine testing of oropharyngeal cancer for HPV • Standardization of HPV detection methods • Prospecting uniform reporting of HPV status by cancer registries • Funding to determine the cost-effectiveness of using Fine Needle Aspiration
Clinical Management	• Standard work-up checklist for HNC Physicians • Enrol patients in clinical trials and functional outcome studies • Evaluation of survivorship care plans • Shared decision-making with patient involvement
Health Economics	• Cost-of-care study of HPV-related HNC • Gender neutral HPV vaccination evaluation • Investment in an awareness campaign
Public Health	• Primary care education of signs and symptoms • Consultation process with medical organisations, advocacy groups, pharmaceutical industry & other stakeholders to implement policy

In conclusion, it is the belief within the clinical and public health community that supportive cancer policy of multidisciplinary collaboration can make a huge difference in tackling this potentially modifiable disease. In the Irish language, the proverb is: "*Ni neart go cur le cheile*" – No strength without unity.

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Appendix

11 Cancer of head and neck

1400 1401 1403 1404 1405 1406 1408 1409 1410 1411 1412 1413
1414 1415 1416 1418 1419 1420 1421 1422 1428 1429 1430 1431
1438 1439 1440 1441 1448 1449 1450 1451 1452 1453 1454 1455
1456 1458 1459 1460 1461 1462 1463 1464 1465 1466 1467 1468
1469 1470 1471 1472 1473 1478 1479 1480 1481 1482 1483 1488
1489 1490 1491 1498 1499 1600 1601 1602 1603 1604 1605 1608
1609 1610 1611 1612 1613 1618 1619 1950 2300 2310 V1001 V1002 V1021

Figure 24: ICD-9-CM codes included in the CCS for head and neck cancer

Extended Estimating Equations

Table 29: Extended estimating equations - stata output

Positive Expenditures	Coeff (SE)
HNC	0.5806**
	(0.2137)
Age	0.0066***
	(0.0007)
Sex	-0.1987***
	(0.0173)
Race	-0.1129***
	(0.0097)
Education	0.1476***
	(0.0152)
Employment	-0.3107***
	(0.0265)
Poverty	0.0594***
	(0.0083)
MSA	0.0266
	(0.0169)
Region	-0.0122*
	(0.0058)
Health Insurance	0.3479***
	(0.0101)
Self-reported Health status	-0.7729***
	(0.0368)
No. of Priority Chronic Conditions	0.3474***
	(0.0080)
Currently Smoking	-0.0783***
	(0.0186)
_cons	-0.4053***
	(0.0641)
lambda	
_cons	0.5228***
	(0.0182)
theta1	
_cons	5.4210***
	(1.6184)
theta2	

```
_cons              0.9095
                  (0.7345)
----------------------------
N                  116759
----------------------------
Standard errors in parentheses
* p<0.05, ** p<0.01, *** p<0.001
```

theta2	Coeff.	Std. Err	z	P>|z|	[95% Conf.	Interval]
_cons	.9094897	.7345398	1.24	0.216	-.5301817	2.349161

Table 29 presents the results of the EEE estimation. The option vf(q) has been specified to estimate the variance as a quadratic function of the conditional mean. Robust variance estimates are also reported by default. The estimate of the Box-Cox parameter for the link function is 0.5228 (95% CI: 0.49 to 0.56), suggesting a square root than a log transformation. Box-cox regression can be where the errors are non-normal and heteroskedastic. The estimate of ν_2(theta2) is 0.90 (95% CI: -0.53 to 2.35) close to Poisson but between Gaussian and Gamma distributions. To compute incremental effects of having head and neck cancer, from the model we can use the post estimation command (pglmpredict):

	Obs	Mean	Std. Dev.	Min	Max
Incremental effect of HNC	116755	2591.17	1020.056	458.648	7804.22
varhnc	116755	1304678	949561.5	99601.98	9026336

The incremental effect is estimated to be $2,591, indicating that the healthcare expenditures of HNC patients are on average $2,591 greater than those without HNC. The variable, varhnc, provides the variance of the incremental effect for each observation conditional on the set of regressors. To obtain the variance of the overall incremental effect, this needs to be combined with the uncertainty associated with the set of regressors. This is given by the variance of the mean incremental effect (22). For the above application the overall standard error of the incremental effect is given by:

$$\text{se (i.e. HNC)} = \sqrt{\frac{1020.06^2}{116755} + 1304678} = 1142.23$$

Table 30: Hurdle model of healthcare utilisation by cancer type in TILDA

	(1) GP_visit	(2) Outpatient	(3) Daycase	(4) IP Admission	(5) ED Visit	(6) Services
Stage 1: Logit						
Age 55 to 59	-0.0131	-0.0583	0.1105	0.1016	0.0886	-0.1511
	(0.1212)	(0.0950)	(0.1113)	(0.1338)	(0.1193)	(0.1089)
Age 60 to 69	0.1103	0.0817	-0.0057	0.0706	-0.1761	-0.4142**
	(0.2114)	(0.1418)	(0.1669)	(0.1929)	(0.1806)	(0.1573)
Age 70 to 79	0.1891	-0.0959	-0.2655	0.0538	-0.4934	-0.4405
	(0.3959)	(0.2479)	(0.2905)	(0.3301)	(0.3145)	(0.2647)
Age 80+	0.2727	-0.2473	-0.8213*	-0.0624	-0.7538	-0.3840
	(0.5557)	(0.3289)	(0.3899)	(0.4339)	(0.4128)	(0.3478)
Female	0.2354**	0.0568	-0.0866	-0.1344	-0.0104	0.0572
	(0.0753)	(0.0550)	(0.0650)	(0.0751)	(0.0690)	(0.0599)
Breast Cancer	**0.5401**	**1.0300*** **	**0.7345*** **	**0.6350** **	**-0.1259**	**0.3550**
	(0.3602)	**(0.1701)**	**(0.1784)**	**(0.1990)**	**(0.2269)**	**(0.1822)**
Prostate Cancer	**1.3572**	**1.3040*** **	**0.2709**	**0.2574**	**0.0489**	**0.0184**
	(0.7318)	**(0.2389)**	**(0.2554)**	**(0.2789)**	**(0.2884)**	**(0.2517)**
Colorectal Cancer	**0.0738**	**1.4624*** **	**1.2812*** **	**1.3114*** **	**0.9067** **	**0.2848**
	(0.5432)	**(0.2922)**	**(0.2708)**	**(0.2787)**	**(0.2827)**	**(0.2901)**
Other Cancer	**0.5397**	**0.6492*** **	**0.8698*** **	**0.6095** **	**0.0722**	**0.2701**
	(0.3164)	**(0.1613)**	**(0.1648)**	**(0.1875)**	**(0.1996)**	**(0.1743)**
Married/LWP	0.1293	0.0459	0.1128	-0.0396	-0.1558*	-0.1864**
	(0.0863)	(0.0585)	(0.0699)	(0.0776)	(0.0714)	(0.0608)
Retired	0.0310	0.1469	0.2252*	0.1124	0.0433	0.3491***
	(0.1126)	(0.0774)	(0.0908)	(0.1073)	(0.0988)	(0.0876)
Unemployed/Student	-0.0616	0.0248	0.0899	0.1489	0.0410	0.1952*

Homemaker	(0.0987)	(0.0746)	(0.0886)	(0.1046)	(0.0943)	(0.0835)
Primary Education Or less	-0.0103 (0.0961)	-0.1180 (0.0626)	-0.1503* (0.0745)	-0.1542 (0.0833)	-0.0424 (0.0771)	-0.2285*** (0.0652)
Town not Dublin	0.1347 (0.1008)	-0.5557*** (0.0692)	-0.1529 (0.0832)	0.1759 (0.0968)	-0.0390 (0.0866)	-0.2962*** (0.0773)
Rural	0.1391 (0.0901)	-0.6402*** (0.0630)	-0.0334 (0.0748)	0.1465 (0.0897)	-0.2101** (0.0807)	-0.2961*** (0.0709)
Medical Card Only	-0.2547 (0.1610)	0.1092 (0.0790)	-0.2746** (0.0928)	-0.1285 (0.0994)	0.0373 (0.0973)	0.2291** (0.0758)
Health Insurance Only	-0.8213*** (0.1552)	-0.1078 (0.0841)	-0.0443 (0.0966)	-0.2149 (0.1098)	-0.1248 (0.1063)	-1.4930*** (0.0903)
No Cover	-1.1645*** (0.1710)	-0.0974 (0.1136)	-0.3996** (0.1387)	-0.8027*** (0.1783)	-0.0712 (0.1425)	-1.1608*** (0.1282)
Chronic_1	0.7756*** (0.0827)	0.5130*** (0.0835)	0.5044*** (0.1040)	0.3270** (0.1233)	0.3716*** (0.1078)	0.2992*** (0.0891)
Chronic_2	1.4359*** (0.1105)	0.8451*** (0.0860)	0.7258*** (0.1068)	0.5738*** (0.1245)	0.4446*** (0.1122)	0.4741*** (0.0921)
Chronic_3	1.9536*** (0.1381)	1.3010*** (0.0845)	1.1138*** (0.1036)	0.8814*** (0.1197)	0.7604*** (0.1077)	0.7121*** (0.0891)
SAH	-1.0105*** (0.1917)	-0.6337*** (0.0753)	-0.4281*** (0.0851)	-0.7769*** (0.0905)	-0.6591*** (0.0868)	-0.2651*** (0.0800)
SAMH	-0.1092 (0.1704)	0.0543 (0.0871)	-0.1490 (0.0973)	0.1178 (0.1094)	-0.1003 (0.1000)	-0.0281 (0.0922)
DISADL	0.4719 (0.2409)	0.4277*** (0.0957)	0.3045** (0.1069)	0.3117** (0.1141)	0.4072*** (0.1088)	0.5390*** (0.1013)
DISIADL	-0.0956 (0.2442)	0.1439 (0.1064)	0.2485* (0.1187)	0.3038* (0.1238)	-0.0080 (0.1227)	0.7691*** (0.1117)
_cons	1.7041*** (0.4825)	-0.6922* (0.2808)	-1.8277*** (0.3285)	-2.1286*** (0.3703)	-1.8807*** (0.3486)	-1.0168*** (0.2959)

Stage 2: Negbinomial

Age 55 to 59	-0.0172	-0.0811	-0.1321	0.5029	0.2396	-0.2432
	(0.0423)	(0.1021)	(0.2123)	(0.2928)	(0.2523)	(0.1291)
Age 60 to 69	-0.1989**	-0.1275	-0.0557	0.4394	-0.5934	-0.0134
	(0.0621)	(0.1481)	(0.3137)	(0.4254)	(0.3962)	(0.1630)
Age 70 to 79	-0.3440**	-0.2185	-0.2183	0.2759	-1.1577	-0.0746
	(0.1064)	(0.2581)	(0.5186)	(0.7100)	(0.6696)	(0.2638)
Age 80+	-0.3558*	-0.2784	-0.5615	0.4418	-0.9690	0.1212
	(0.1401)	(0.3398)	(0.7105)	(0.9314)	(0.8766)	(0.3342)
Female	-0.0385	-0.0886	-0.2917*	-0.3478*	-0.0304	-0.0369
	(0.0239)	(0.0579)	(0.1293)	(0.1586)	(0.1431)	(0.0603)
Breast Cancer	**0.1911****	**0.5409*****	**0.6142***	**1.0470****	**-0.0512**	**0.0480**
	(0.0722)	**(0.1348)**	**(0.3004)**	**(0.3715)**	**(0.4891)**	**(0.1613)**
Prostate Cancer	**0.3869*****	**0.5009****	**1.2123****	**0.5722**	**0.6217**	**0.0834**
	(0.0935)	**(0.1720)**	**(0.4292)**	**(0.5317)**	**(0.5978)**	**(0.2272)**
Colon Cancer	**0.3565****	**0.6257****	**0.6876**	**0.4855**	**-0.0366**	**0.1526**
	(0.1119)	**(0.1928)**	**(0.3786)**	**(0.4332)**	**(0.5045)**	**(0.2133)**
Other Cancer	**0.2115****	**0.4509*****	**1.1245*****	**0.5881**	**0.3913**	**-0.0234**
	(0.0679)	**(0.1359)**	**(0.2619)**	**(0.3401)**	**(0.3760)**	**(0.1479)**
Married/LWP	-0.0743**	-0.0045	0.0343	-0.0816	0.1377	-0.2010***
	(0.0248)	(0.0597)	(0.1332)	(0.1637)	(0.1501)	(0.0584)
Retired	0.0898**	0.3277***	0.1296	-0.0876	0.2618	0.0786
	(0.0340)	(0.0838)	(0.1757)	(0.2369)	(0.2079)	(0.1076)
Unemployed/Student /Homemaker	0.1859*** (0.0326)	0.3119*** (0.0806)	0.1903 (0.1697)	0.1373 (0.2340)	0.1572 (0.1962)	0.0478 (0.1051)
Primary Education Or Less	0.0726** (0.0261)	0.0217 (0.0644)	-0.3325* (0.1406)	-0.3593* (0.1688)	0.0404 (0.1600)	-0.0550 (0.0613)
Town not Dublin	0.1278***	-0.1003	-0.0720	0.0566	0.2930	-0.0700
	(0.0312)	(0.0702)	(0.1559)	(0.2049)	(0.1866)	(0.0733)
Rural	0.1242***	-0.1390*	-0.1233	0.2416	0.3547*	-0.1351*
	(0.0286)	(0.0636)	(0.1382)	(0.1902)	(0.1707)	(0.0685)
Medical Card	0.0617	-0.0391	-0.0910	0.0959	-0.2962	-0.1241

Only	(0.0318)	(0.0788)	(0.1663)	(0.1973)	(0.1930)	(0.0666)
Health Insurance	-0.3736***	-0.1440	-0.2115	0.1505	-0.6430**	-0.4604***
Only	(0.0354)	(0.0849)	(0.1708)	(0.2297)	(0.2180)	(0.1122)
No Cover	-0.4360***	-0.3206*	-0.2412	0.3654	-0.2637	-0.7687***
	(0.0512)	(0.1248)	(0.2721)	(0.3924)	(0.2898)	(0.2018)
Chronic_1	0.2789***	0.0205	-0.1114	-0.0532	0.0027	0.1123
	(0.0373)	(0.1019)	(0.2147)	(0.2698)	(0.2462)	(0.1146)
Chronic_2	0.4888***	0.0137	0.1856	-0.3645	-0.0189	-0.0020
	(0.0379)	(0.1031)	(0.2166)	(0.2721)	(0.2561)	(0.1160)
Chronic_3	0.6129***	0.1803	0.2643	-0.3529	0.2973	0.2767**
	(0.0369)	(0.0975)	(0.2062)	(0.2549)	(0.2379)	(0.1064)
SAH	-0.3898***	-0.3880***	-0.4993***	-0.7646***	-0.3699*	-0.3280***
	(0.0308)	(0.0673)	(0.1392)	(0.1754)	(0.1651)	(0.0658)
SAMH	-0.1241***	-0.0457	-0.2300	0.0324	0.0510	-0.1282
	(0.0354)	(0.0807)	(0.1665)	(0.2134)	(0.1920)	(0.0735)
DISADL	0.2274***	0.0761	0.2207	0.3585	0.0617	0.3663***
	(0.0385)	(0.0823)	(0.1740)	(0.2131)	(0.2083)	(0.0720)
DISIADL	0.1082*	0.0782	0.4294*	0.1998	0.6693**	0.3017***
	(0.0423)	(0.0916)	(0.1904)	(0.2249)	(0.2192)	(0.0754)
_cons	0.9425***	0.7789**	-2.3776	-13.0120	-12.6036	0.2678
	(0.1198)	(0.2902)	(2.0030)	(42.2791)	(26.1817)	(0.2872)
lnalpha						
_cons	-0.7286***	0.2050	2.9860	12.8388	11.7693	-1.5233***
	(0.0387)	(0.1134)	(2.0677)	(42.2710)	(26.1704)	(0.2690)
N	8112.0000	8112.0000	8112.0000	8112.0000	8112.0000	8112.0000
ll	-18321.5526	-9220.0022	-5134.0790	-3826.8270	-4340.8574	-6483.4903
aic	36753.1053	18550.0045	10378.1580	7763.6540	8791.7148	13076.9805
bic	37138.1658	18935.0649	10763.2185	8148.7145	9176.7753	13462.0410

Coefficients of models are given with standard errors in parentheses.
* p<0.05, ** p<0.01, *** p<0.001

Table 31: Average marginal effects on receiving [1st part -logit] and on condition ally positive number of GP visits and outpatient office visits [2nd part - Zero Truncated Negative Binominal (ZTNB)]

Characteristic	GP Visit		Outpatient Office Visit	
	1st Part: logit Marginal effect [se]	2nd Part: ZTNB Marginal effect [se]	1st Part: logit Marginal effect [se]	2nd Part: ZTNB Marginal effect [se]
Age 50-54	REF	REF	REF	REF
Age 55-59	0.053	0.167	-0.013	-0.123
	[0.009]	[0.151]	[0.016]	[0.149]
Age 60-69	0.026**	-0.165	0.010	-0.212
	[0.095]	[0.141]	[0.016]	[0.145]
Age 70-79	0.046***	-0.156	-0.027	-0.356*
	[0.013]	[0.168]	[0.019]	[0.169]
Age 80+	0.056***	0.189	-0.060**	-0.423*
	[0.016]	[0.218]	[0.023]	[0.188]
Male	REF	REF	REF	REF
Female	0.021**	-0.155	0.014	-0.140
	[0.007]	[0.093]	[0.011]	[0.098]
Never smoked	REF	REF	REF	REF
Past smoker	-0.007	0.121	0.027*	-0.009
	[0.008]	[0.097]	[0.011]	[0.101]
Current smoker	-0.052***	-0.050	-0.042**	0.016
	[0.011]	[0.123]	[0.014]	[0.135]
No cancer	REF	REF	REF	REF
Time since cancer diagnosis				
0/1 years	0.076**	2.475***	0.460***	1.750***
	[0.028]	[0.55]	[0.047]	[0.476]
2/5 years	0.048	1.188***	0.195***	1.079**
	[0.025]	[0.343]	[0.037]	[0.344]
6/10 years	0.049	-0.164	0.0119**	0.662
	[0.032]	[0.337]	[0.046]	[0.399]
11 years +	0.030	1.055**	0.140***	0.579
	[0.027]	[0.389]	[0.041]	[0.347]
Not married	REF	REF	REF	REF
Married/living with	0.009	-0.300	0.008	0.008
partner	[0.009]	[0.098]	[0.011]	[0.101]
Employed	REF	REF	REF	REF
Retired	0.007	0.414**	0.028	0.571***
	[0.010]	[0.133]	[0.015]	[0.152]
Unemployed/Student	-0.003	0.775***	0.008	0.567***
/Homekeeper	[0.010]	[0.137]	[0.014]	[0.159]
Less than primary education	REF	REF	REF	REF
More than primary	0.002	0.303***	-0.021	0.039
education	[0.009]	[0.103]	[0.012]	[0.110]
Dublin	REF	REF	REF	REF
Other town	0.013	0.512***	-0.100***	-0.160
	[0.009]	[0.128]	[0.012]	[0.115]
Rural	0.011	0.481	-0.125***	-0.234*
	[0.009]	[0.113]	[0.012]	[0.106]
Dual cover	REF	REF	REF	REF
Medical card only	-0.201	0.230	0.025	-0.064
	[0.016]	[0.012]	[0.015]	[0.133]

Health insurance only	-0.081***	-1.369***	-0.022	-0.230
	[0.025]	[0.120]	[0.016]	[0.138]
No cover	-0.135***	-1.424***	-0.013	-0.464**
	[0.024]	[0.138]	[0.021]	[0.164]
No chronic conditions	REF	REF	REF	REF
1	0.071***	1.188***	0.096***	0.025
	[0.007]	[0.175]	[0.016]	[0.174]
2	0.112***	2.230***	0.164***	0.008
	[0.007]	[0.205]	[0.017]	[0.175]
3	0.135***	2.619***	0.268***	0.296
	[0.007]	[0.178]	[0.018]	[0.167]
Self-rated Health				
Fair/Poor	REF	REF	REF	REF
Excellent/Very good/	-0.076***	-1.663**	-0.135***	-0.717***
good	[0.010]	[0.145]	[0.017]	[0.136]
Self-rated mental health				
Fair/Poor	REF	REF	REF	REF
Excellent/Very good/good	-0.016	0.477***	0.008	-0.085
	[0.015]	[0.149]	[0.017]	[0.142]
Activates of daily living				
No Limitation	REF	REF	REF	REF
>1 limitation	0.040*	0.997***	0.086***	0.134
	[0.018]	[0.178]	[0.020]	[0.147]
Instruments of daily living	REF	REF		
No limitation			REF	REF
>1 limitation	-0.007	0.415*	0.029	0.112
	[0.024]	[0.177]	[0.021]	[0.163]
N	8111	7092	8111	2588

*** P>0.001 ** P>0.01 * P>0.05

Table 32: Bivariate probit models for healthcare utilisation stratified by type of cancer in TILDA*

Characteristic	GP Visits	Inpatient stay	Outpatient – Daycase	Outpatient - Office Visit	Emergency Room Visit	Public Services
No Cancer	***REF***	***REF***	***REF***	***REF***	***REF***	***REF***
Time Since **Breast** Cancer Diagnosis						
0-1years	0.071	0.334***	0.212***	0.388***	0.045	0.297***
	(0.089)	(0.052)	(0.064)	(0.096)	(0.066)	(0.080)
2-5years	0.133	0.070	0.157***	0.221***	-0.004	0.074
	(0.074)	(0.038)	(0.084)	(0.060)	(0.048)	(0.054)
6-10years	0.008	-0.066	0.113**	0.085	-0.002	-0.008
	(0.059)	(0.059)	(0.051)	(0.066)	(0.055)	(0.060)
11+years	0.030	0.022	-0.017	0.227***	-0.034	0.006
	(0.052)	(0.040)	(0.051)	(0.080)	(0.050)	(0.052)
N		7784	7784	7784	7784	7784
σ (GP, healthcare service)		0.316***	0.280***	0.307***	0.248***	0.105***
		(0.039)	(0.033)	(0.027)	(0.034)	(0.031)
Log-likelihood		-5237.33	-5878.37	-6895.57	-5650.16	-6351.80
Time Since **Prostate** Cancer Diagnosis						
0-1years	0.093	0.230***	0.231**	0.611	0.057	0.050
	(0.088)	(0.068)	(0.068)	(0.121)	(0.072)	(0.081)
2-5years	0.099	-0.073***	-0.023	0.182***	0.001	-0.002
	(0.085)	(0.054)	(0.055)	(0.066)	(0.053)	(0.061)
6-10years	0.888	-0.057	0.019	0.189	-0.048	0.050
	(162.4)	(0.079)	(0.080)	(0.098)	(0.087)	(0.088)
11+years	0.843	0.055	-0.103	0.202	0.110	-0.106
	(183.4)	(0.089)	(0.131)	(0.129)	(0.094)	(0.031)
N		7707	7707	7707	7707	7707
σ (GP, healthcare service)		0.323***	0.276***	0.303***	0.250***	0.104***
		(0.044)	(0.036)	(0.031)	(0.034)	(0.031)
Log-likelihood		-5178.19	-5809.66	-6824.95	-5598.40	-6279.45
Time since **Colon** Cancer Diagnosis						
0-1years	-0.004	0.459***	0.323**	0.523*	0.261	0.354***
	(0.104)	(0.108)	(0.100)	(0.177)	(0.185)	(0.138)
2-5years	0.039	0.115**	0.203***	0.374***	0.169	-0.057
	(0.080)	(0.055)	(0.066)	(0.094)	(0.121)	(0.087)
6-10years	0.786	0.138**	0.243***	0.148	0.134	0.036
	(78.89)	(0.064)	(0.081)	(0.107)	(0.120)	(0.097)
11+ years	-0.083	0.062	0.045	0.251**	0.159	0.038
	(0.786)	(0.067)	(0.082)	(0.110)	(0.128)	(0.093)
N		7680	7680	7680	7680	7680
σ (GP, healthcare service)		0.320***	0.280***	0.303***	0.253***	0.106***
		(0.044)	(0.035)	(0.030)	(0.030)	(0.031)
Log-likelihood		-5810.33	-5811.36	-6814.76	-5602.68	-6269.30

Time Since '**Other Cancer'** Diagnosis						
0-1 years	0.849	0.202***	0.254***	0.339***	0.103***	0.048
	(99.45)	(0.390)	(0.049)	(0.071)	(0.030)	(0.060)
2-5years	0.000	-0.044	0.049	0.097	-0.074	-0.019
	(0.048)	(0.044)	(0.044)	(0.054)	(0.052)	(0.049)
6-10years	0.058	0.092**	0.214**	0.142	0.048	0.193***
	(0.071)	(0.050)	(0.055)	(0.075)	(0.057)	(0.067)
11+years	0.063	0.048	0.036	0.019	0.003	0.021
	(0.047)	(0.043)	(0.047)	(0.058)	(0.048)	(0.054)
N		7802	7802	7802	7802	7802
σ (GP, healthcare service)		0.330***	0.271***	0.306***	0.251***	0.109***
		(0.040)	(0.035)	(0.031)	(0.036)	(0.031)
Log-likelihood		-5248.92	-5897.86	-6912.89	-5659.51	-6353.84

* P<0.05, **P<0.01 ***P<0.001 Coefficients of models are given with standard errors in parentheses. Models controls for predisposing, enabling and need characteristics included in Table 15.