Generalisability of pharmacoepidemiological studies using restricted prescription data.

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Abstract

Background

Linking medication databases to disease registries enables population-based pharmacoepidemiology research. In Ireland, country-wide dispensing data is available only from the means-tested government-medical cards scheme.

Aim

Gender was previously identified as predictor of card status so we aimed to compare women with and without medical cards at the time of ovarian cancer diagnosis.

Methods

Ovarian cancers diagnosed 2001-2010 were identified from the National Cancer Registry Ireland. Age, region, deprivation, smoking, employment and marital status were evaluated using logistic regression for associations with card status. Cumulative incidence of *de novo* card receipt post-diagnosis was assessed.

Results

1778 (52%) of 3396 women with incident ovarian cancer had a card at diagnosis (<70: 33%; 70+: 87%). Within those <70, all variables were significantly associated with card status at diagnosis. 52% of those without a card at diagnosis received one post-diagnosis.

Conclusions

Although medical card coverage within ovarian cancer patients is similar to the general population, various factors predict card status. Particularly within those under 70, external validity needs to be considered when interpreting pharamcoepidemiological analyses using these data.

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Introduction

The evaluation of drug use and effects in populations is known as pharmacoepidemiology [1]. Research in this field can: shed light in areas where clinical trials are not possible or considered premature; lead to discovery of previously undetected adverse or beneficial effects of drugs; and generate hypotheses for future research.

The Irish Health Service Executive reimburses pharmacies for prescriptions dispensed to medical card holders via the Primary Care Reimbursement Service (PCRS). In so doing, the service records prescriptions dispensed to all card holders. This database has been acknowledged as one of the pillars of pharmacoepidemiological research in Ireland [2] and, when linked with population-based disease registers, enables research that could be otherwise very difficult or impossible to conduct.

Ireland has contributed to the cancer pharmacoepidemiology field since 2007 when prescription card data was first combined with information on incident breast, prostate and colorectal cancers recorded by the National Cancer Registry (hereafter, the registry). Resulting studies have evaluated associations between cancer outcomes and various drugs including: aspirin, metformin, digoxin and beta-blockers [3–8]. Similar information is now available for other cancers, including cancer of the ovary.

Due to the source of the data, prescribing records are not available for all cancer patients, only those with a medical card. Thus, pharmacoepidemiological research can only be conducted in the population of patients who meet the age and income thresholds of the medical card scheme. The exact thresholds have changed over time but, as of January 2014, were (for a single person): €184/week (≤65 years), €201.50 (66-69 years) and €500/week (≥70 years) [9]. Pre-2009 everyone aged 70+ was eligible for a card. In 2011, the thresholds resulted in roughly one third of the population <70 having a card [10, 11]. Factors such as: area of residence, gender, marital and smoking status can also predict whether a cancer patient has medical card [12], but to date these associations have only been evaluated in colorectal cancer. Discretionary cards can be awarded following cancer diagnosis on hardship grounds.

The aim of this study was to evaluate the differences between women with and without medical cards at the time of ovarian cancer diagnosis. Understanding the nature of this selection is essential to the generalisation of findings from subsequent pharmacoepidemiology studies.

Methods

Details of individuals who held a medical card any time prior to April 2013 were obtained from the PCRS and linked to registry records for women with primary invasive ovarian cancer (ICD-10 code C56) diagnosed 2001-2010. Matching was carried out using probabilistic matching based on name, date of birth, address and other available information, and was supplemented with manual review of ambiguous records.

Demographic characteristics for each woman diagnosed with ovarian cancer (age, health board, marital status, employment and smoking status) were abstracted from the registry. Local area of residence at diagnosis was linked to 2006 census data and deprivation quintile estimated based on the established index [13].

Card coverage at the time of diagnosis was determined based on medical card start and stop dates, taking into account multiple or recurrent cards. Missing start dates were assumed to be prior to the year 1980 and cards without expiry dates were assumed to be ongoing. Duration of card history prior to diagnosis was computed.

Among women diagnosed with ovarian cancer under 70 (the age at which the income threshold increases), logistic regression was used to compare characteristics of those with and without medical cards. Age was included as a categorical variable (</≥ 60 years). Smoking and employment status were both categorised as current at the time of diagnosis vs. not. Marital status was coded as currently, previously or never married. Local area deprivation was considered as present in areas above the 2nd quintile of the index (higher 60%),

All women were assumed to be alive at 31st December 2012 unless matched to a death certificate or other death notification. The Kaplan-Meier method was used to estimate all-cause

survival by card status stratified for age at diagnosis (</≥70 years) and Cox regression used to estimate the effect of having a card on mortality adjusted for characteristics. Hazard ratios adjusted for characteristics (AHR) and 95% confidence intervals (CI) were computed.

Allocation of discretionary cards post-diagnosis was evaluated amongst those who did not have one at the time of diagnosis. Time to receipt of card (after diagnosis) was computed censoring at end of follow-up, considering death a competing risk (using the %CUMINCID macro in SAS version 9.4) [14].

Results

3396 women were diagnosed with ovarian cancer in Ireland between 2001 and 2010. Of these women, 1778 (52%) were identified as having a medical card at the time of diagnosis (<70 at diagnosis: 33%; 70+ at diagnosis: 86%). Most card holders (92%) had had them for at least 12 months prior to diagnosis; the median card history was 10 years (excluding 27% of cards with unknown start dates).

All demographic variables evaluated were strongly associated with card status at the time of diagnosis in women aged under 70 (Table 1). In multivariate models, card holders were significantly more likely to be current smokers, aged 60-69, previously married and living in more socially deprived areas. Women in employment or who were married at the time of diagnosis were significantly less likely to have cards.

Women aged 70+ at diagnosis had worse survival than those diagnosed younger (Figure 1). In this older group, no survival difference was observed between those with and without cards (AHR=1.04, 95%CI 0.86,1.25). Among women <70, median survival was substantially shorter among card holders than those without cards (card: 2.3 years, 95%CI 1.9, 2.7; no card: 4.4 years, 95%CI 3.9, 5.1). Adjusting for confounders, there remained a significant association between card status and poorer survival (AHR=1.37, 95%CI 1.21, 1.55).

Of the women without cards at the time of diagnosis, 52% subsequently went on to receive one within our observation period. Median time to card receipt (taking into account women who had died) was 19 months. The percentage of women without cards who went on to receive one within 3 months of diagnosis was 8% in the 70+ group and 36% in those aged <70.

Discussion

Our study found that medical card status at the time of diagnosis (87% in women 70 and over, 33% in those younger) was broadly consistent with population figures for Ireland (~97%, 33%) [10, 11]. This indicates, to some extent, that risk of ovarian cancer is broadly independent of income. We observed strong associations between card status and age (<70/70+). Within those <70 at diagnosis, local area deprivation, employment, smoking and marital status all predicted card receipt. This suggests that pharmacoepidemiology studies restricted to the medical card population need to consider whether this potential selection bias may affect the generalisability of results.

Among women diagnosed with ovarian cancer under 70 years, local area deprivation, smoking, employment and marital status variables were also all associated with survival. We found that even after adjusting for these confounders, women with medical cards at diagnosis had worse all-cause survival. Card holders, by definition, are less likely to be working than those without cards; they may not work because of poor health and comorbid conditions and it may be these additional factors which are influencing survival in this group. While income (which largely determines medical card eligibility in this group) may have a direct impact on overall health, time to diagnosis, treatment, and cancer survival, it is also a proxy for socio-economic status. In this regard, the SAHRU deprivation index [13] (and other similar indices) is likely to result in misclassification of socio-economic status for cases as they are measured at the area, rather than the individual, level. The percentage of card-holders in all quintiles of the SAHRU index ranged between 47-53% suggesting card status may be a valuable addition to the index.

Evaluation of card allocation post-diagnosis demonstrated that a significant proportion of women without a card at diagnosis subsequently receive a card. The figure was higher than in a

similar study of colorectal cancers diagnosed 2002-2006 [12]. This difference may reflect either the different age distribution of ovarian and colorectal cancer patients, or the recent increase in eligibility due to economic recession [10].

This study evaluated the complete ovarian cancer population but has some limitations. There are a number of issues relating to card and registry data that could affect the matching process: for example, infrequently multiple cards exist for a single person; and, on rare occasions, card numbers have been reused by multiple people. These could mean that we have slightly under- or over-estimated the rate of card holders. Start dates were unavailable for 27% of cards. Depending on the route to diagnosis, the date of diagnosis recorded in the registry may differ from the true date of diagnosis.

Given the differences between card holders and non-holders in those under 70, it is important to ask whether useful information be obtained from pharmacoepidemiology studies based on these data. If we can assume the therapeutic effects of medications are the same in those with and without cards – i.e. that there is no modification of the effect due to differences in age, smoking status or overall health for example – the results found in those with cards should apply to the whole population. Having a medical card may make people more likely to visit the doctor[15] and thus influence the frequency with which prescriptions are started. This could mean that card holders and non-holders differ in time to medication after the start of a particular condition. This should not impact results of pharamcoepidemiological studies provided an analysis method is used. However, it could limit study generalisability to the wider population.

In conclusion, this study investigated patterns of medical cards within the Irish ovarian cancer population. We observed similar rates of medical cards amongst women diagnosed with ovarian cancer to that in the Irish female population. The card eligibility income threshold creates differences in the characteristics of the patients for whom prescription data is available and those for whom it is not. Moreover, amongst those under the 70 year threshold, card status is associated with all-cause survival even after adjusting for confounders. The effect of this selection needs to be considered when interpreting pharmacoepidemiological research carried

out with these data - methods to enable generalisation to the wider population should be investigated.

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Fig.1 – Flowchart of registry and card matching and status at diagnosis

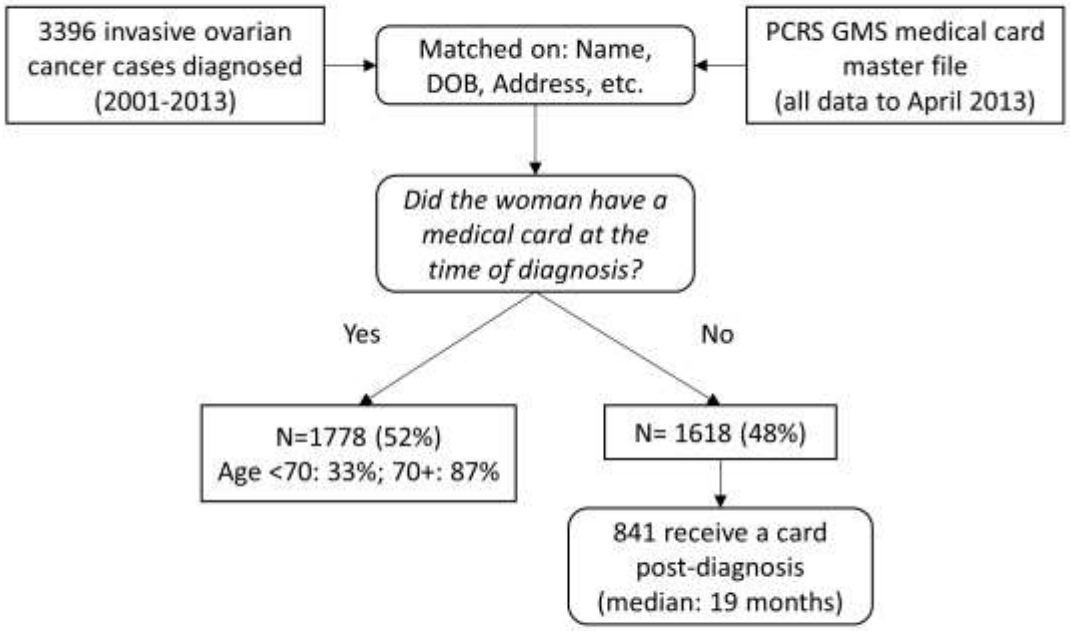

Fig.2 – All-cause survival by age and card status at diagnosis

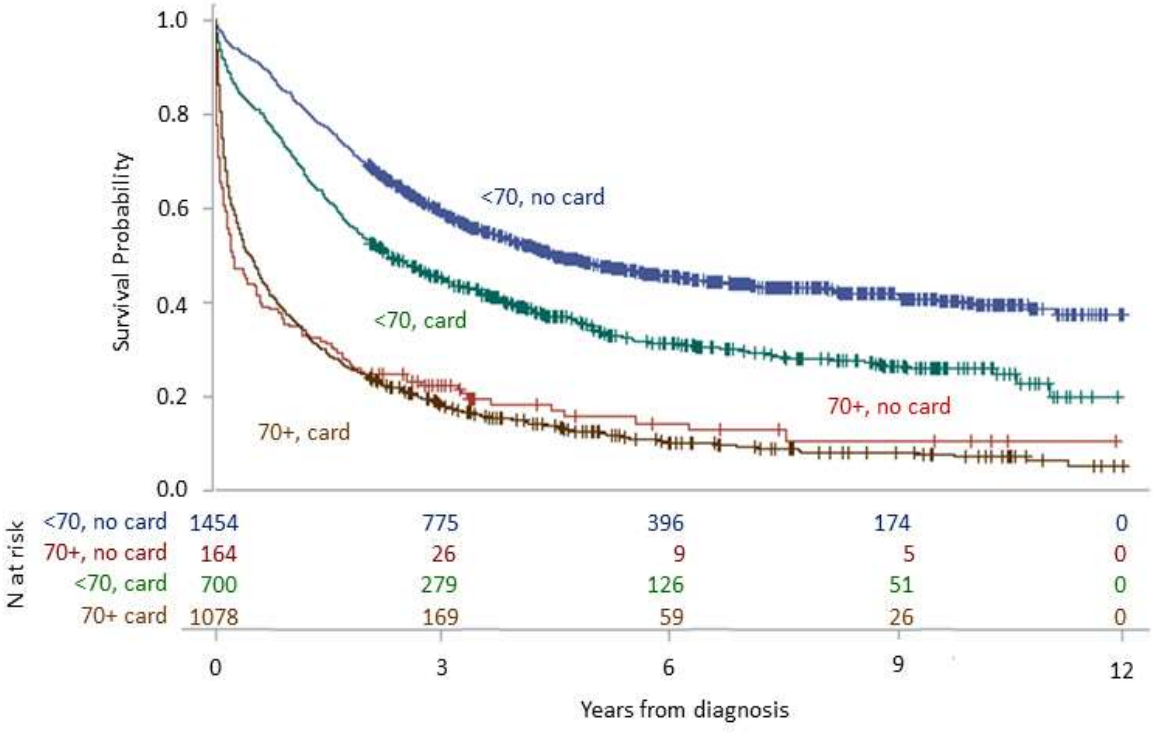

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Table 1 - Patient characteristics of women diagnosed with ovarian cancer <70 years and their adjusted odds (with 95% confidence intervals) of being a cardholder at diagnosis.

Variable (at diagnosis)		N	% with card at diagnosis	OR (95%CI)	p-value	AOR (95%CI)[a]	p-value
Age	<60	1,325	24.9		<.0001		<.0001
	≥60	829	44.6	2.43 (2.02, 2.93)		1.89 (1.54, 2.32)	
Local area deprivation	Not deprived	911	22.7		<.0001		<.0001
	Deprived	1,243	39.7	2.22 (1.93, 2.69)		1.98 (1.61, 2.44)	
Employed	No	1,544	38.8		<.0001		<.0001
	Yes	610	16.6	0.31 (0.25, 0.40)		0.31 (0.24, 0.40)	
Married	Never	473	34.5		<.0001		<.0001
	Currently	1,378	26.8	0.70 (0.56, 0.88)		0.50 (0.39, 0.65)	
	Previously	303	55.4	2.33 (1.74, 3.13)		1.77 (1.28, 2.45)	
Smoking status	No	1,527	31.0		0.019		0.027
	Current	627	36.0	1.27 (1.04, 1.54)		1.28 (1.03, 1.58)	

[a] Odds Ratios (OR) adjusted for all variables shown in table and area (not displayed)

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