Associations between commonly-prescribed medicines and cancer risk: a series of nested case-control studies

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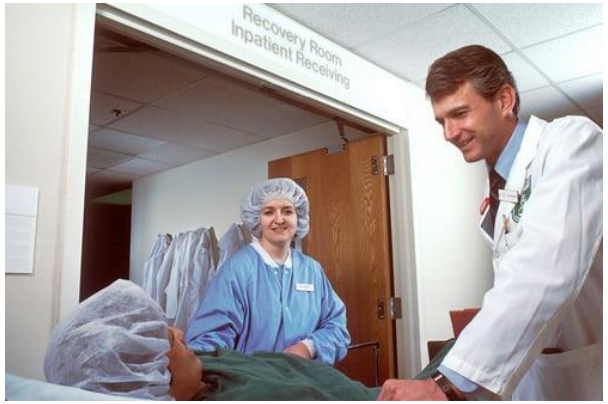

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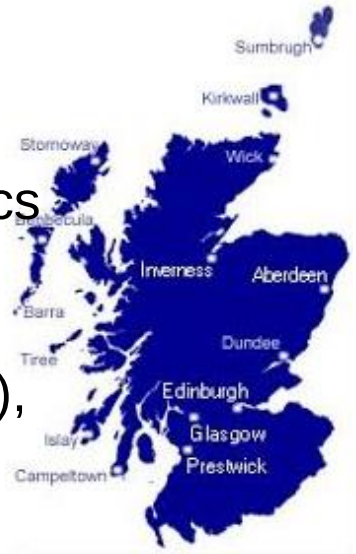
Background

- Medicines can have unintended effects, identified many years after licensing
- Screening studies have been used to identify medications associated with a higher or lower risk of cancer in countries such as the USA, Denmark, Norway [1-3]
- These are limited in terms of their lack of controlling for site-specific comorbidities and lifestyle factors (e.g. smoking)
- **Aim:** to determine novel candidate medications associated with a higher or lower risk of cancer in a UK sample

[1] Friedman et al. Screening pharmaceuticals for possible carcinogenic effects: initial results for drugs not previously screened: Cancer Causes Control (2009): 20:1821-1835
[2] Pottegȧrd et al. Identification of Associations between Newly Prescribed Medications and Cancer: A Nationwide Screening Study: Ebiomedicine 7 (2016) 73-79
[3] Andreassen et al. identification of potential carcinogenic and chemopreventative effects of prescription drugs: a protocol for a Norwegian registry0-based study. BMJ Open 2019: 9: e028504

Methods



- A series of nested case-control studies using the Primary Care Clinical Informatics Unit (PCCIUR) database (over 2 million Scottish patients)

- Each cancer case was matched with up to five controls based on age (+-5 years), gender, general practice and year of registration

- Medication use was determined during the exposure period: within each matched set the exposure period began on **either** 1 January 1993 **or** the latest registration date after 1 January 1993. Finished 1 year prior to diagnosis of case

- Associations between the most commonly-prescribed medications (approx. 250 medicines per site) and specific cancers were estimated using conditional logistic regression adjusting for comorbidities (with and without smoking).

- <u>Signals:</u>

1 OR >=1.25 or OR <=0.8; 2 p<=0.01; 3 exposure-response relationship

Results (updated as of 1 June 2020)

- 22 cancer sites e.g. breast (12,269 cases), lung (9,409 cases)

Variable	Category	Cases (n=62,019) Median (IQR)	Controls (n=276,580) Median (IQR)
Exposure period (years)		8.1 (5.5,11.0)	8.1 (5.5,11.0)
Year of diagnosis/index date		2005 (2002,2007)	2005 (2002,2007)
Age at diagnosis/index date		68 (58,76)	65 (55,74)
Variable	**Category**	**Cases (n=62,019) n (%)**	**Controls (n=276,580) n(%)**
Gender	Male	29,653 (47.8%)	128,988 (46.6%)
	Female	32,366 (52.2%)	147,592 (53.4%)
Smoking status	Never smoked	19,058 (30.7%)	97,246 (35.2%)
	Ex-smoker	14,716 (23.7%)	58,984 (21.3%)
	Current smoker	15,877 (25.6%)	57,734 (20.9%)

Results (updated as of 1 June 2020)

- 5,622 medicine-cancer associations were investigated

Exposure	Adjusted for	No. signals
>=1 item of medicine	Comorbidities *	118
>=1 item of medicine	Comorbidities * & smoking	79
>=6 items of medicine (v<6 items)	Comorbidities *	118
>=6 items of medicine (v<6 items)	Comorbidities * & smoking	85

- 235 unique signals, 49 identified only after adjusting for smoking
- 173 signals associated with increased cancer risk, 62 with lower cancer risk
- Results similar following sensitivity analyses e.g. varying lag time to 2 years, imputation of missing smoking values

* Charlson comorbidities + site-specific conditions

Background

- Signals identified can be classified as follows:

Group	Medicine	Cancer	Model	OR (95%CI), p-values
1:medicines with known cancer associations	estrogen-hormone replacement therapy	breast	Comorbidity adjusted, >=1 item	1.26 (1.19,1.33) p<0.001
2:associations which may not be directly causal	omeprazole*	oesophageal	Comorbidity & smoking adjusted, >= 6 items	1.30 (1.13,1.49) p<0.001
3:signals to be investigated	clopidogrel**	pancreas	Comorbidity adjusted, >=6 items	2.38 (1.46,3.88) p=0.001

- Strengths include: long follow-up time, adjustment for site-specific risk factors and smoking, first UK screening study

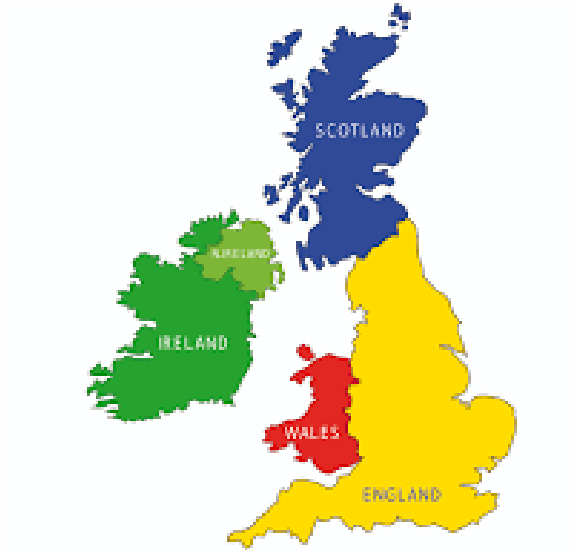
- Limitations include: exploratory analysis/multiple testing with increased risk of chance findings, models not tailored to individual medicine/cancer site combinations

* used to treat gastroesophageal reflux & oesophagitis, precursors of oesophageal cancer

** causes inflammation, which in turn is linked to cancer

Conclusions

- This study should provide reassurance to patients and clinicians that the majority of medicines are not associated with an increased risk of cancer
- Increased polypharmacy means there is a need to identify medicines with cancer-limiting or cancer-increasing potential
- The signals identified merit more detailed study in other clinical databases and in preclinical studies, to identify whether there are potential casual mechanisms of relevance



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