---

**Article:**
Fairhurst, Caroline orcid.org/0000-0003-0547-462X, Watt, Ian orcid.org/0000-0002-3147-8299, Martin, Fabiola orcid.org/0000-0001-6606-8065 et al. (2 more authors) (2014) Exposure to sodium channel-inhibiting drugs and cancer survival : protocol for a cohort study using the QResearch primary care database. BMJ Open. e006604. ISSN 2044-6055

https://doi.org/10.1136/bmjopen-2014-006604

---

**Exposure to sodium channel-inhibiting drugs and cancer survival: protocol for a cohort study using the QResearch primary care database**

Caroline Fairhurst[1], Ian Watt[1,2], Fabiola Martin[2,3], Martin Bland[1], and William J. Brackenbury[3*]

[1]Department of Health Sciences, University of York, York, UK

[2]Hull York Medical School, York, UK

[3]Department of Biology, University of York, York, UK

*Corresponding author:

William J. Brackenbury

Department of Biology, University of York, Heslington, York, YO10 5DD, UK

E-mail: william.brackenbury@york.ac.uk

Telephone: +44 (0) 1904 328 284

Keywords: Anticonvulsants / Breast neoplasms / Colonic neoplasms / Prostatic neoplasms / Sodium channels

Word count, excluding title page, abstract, references, figures and tables: 2292.

**ABSTRACT**

**Introduction:** Metastasis from solid tumours is associated with significant morbidity and mortality, and is the leading cause of cancer-related deaths. Voltage-gated sodium channels (VGSCs) are drug targets for the treatment of epilepsy. VGSCs are also present in cancer cells, where they regulate metastatic cell behaviours, including cellular movement and invasion. Treating cancer cells with the VGSC-inhibiting anticonvulsant phenytoin reduces cellular invasion and migration. Together, these suggest that VGSCs may be useful targets for inhibiting metastasis. The purpose of this study is to test the hypothesis that use of VGSC-inhibiting drugs will reduce metastasis, and therefore increase survival time in cancer patients.

**Methods and analysis:** A cohort study based on primary care data from the QResearch database will include patients with one of three common tumours: breast, bowel, and prostate. The primary outcome will be overall survival from date of cancer diagnosis. Cox proportional hazards regression will be used to compare the survival of cancer patients taking VGSC-inhibiting drugs (including anticonvulsants and Class I antiarrhythmic agents) with cancer patients not exposed to these drugs, adjusting for age and sex. Exposure to VGSC-inhibiting drugs will be defined as having at least one prescription for these drugs prior to cancer diagnosis. High and low exposure groups will be identified based on length of use. A number of sensitivity and secondary analyses will be conducted.

**Ethics and dissemination:** The protocol has been independently peer-reviewed and approved by the QResearch Scientific Board. The project has also been approved by the University of York Ethical Review Process. The results will be presented at international conferences and published in an open access peer-reviewed journal, in accordance with the STROBE criteria.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- Primary care research data
- Large sample size and statistical power
- Planned sensitivity analyses
- Prescription-based study
- No direct information on metastasis, estimation is *via* overall survival
- Some variables of interest may be missing and/or poor quality in GP data

## INTRODUCTION

Bowel, breast and colon cancer are common cancers, which if diagnosed late have often already spread to secondary sites (metastasised). Metastasis is associated with significant morbidity and mortality. Metastasis is the leading cause of cancer-related deaths[1] because a metastatic cancer is rarely amenable to cure, and interventions are largely limited to palliation.[2] Therefore, there is an urgent need to identify and/or develop new metastasis prevention strategies.

The classical role of voltage-gated sodium channels (VGSCs) is to transmit action potentials in electrically excitable cells, e.g. neurons and cardiomyocytes.[3] VGSCs also regulate neuronal growth and migration.[4-7] Related to these functions, VGSCs are clinical targets for a range of disorders, including epilepsy, cardiac arrhythmias, neuropathic pain and depression.[8] The mode of action of a number of commonly prescribed antiepileptic drugs (anticonvulsants), including phenytoin, lamotrigine, carbamazepine and valproate, is to inhibit VGSCs.[9] Similarly, the principal mode of action of Class I antiarrhythmic drugs is to inhibit VGSCs.[10]

More recently, VGSCs have been identified in cells from a number of major cancers, including carcinomas of the breast, prostate and colon.[11 12] In these cells, VGSCs promote *in vitro* cellular behaviours that are associated with metastasis, including migration and invasion.[13-18] Overexpression of the VGSC β1 subunit in breast cancer cells increases metastasis in mice.[19-21] The VGSC-inhibiting anticonvulsant phenytoin significantly reduces migration and invasion of metastatic breast and prostate cancer cells *in vitro*.[22 23] Together, these data suggest that VGSCs may be useful targets for anti-metastatic therapy, and that VGSC-inhibiting drugs may improve survival from certain cancers.[11 24] Although the effect of several anticonvulsants on risk of developing various cancers has been studied before (reviewed in[25]), the relationship between VGSC-inhibiting drugs and survival of cancer patients has not been investigated.

The purpose of this study is to test the hypothesis that use of VGSC-inhibiting drugs will predict increased time to metastasis and thus improved survival time in cancer patients. The objectives are to investigate:

- The relationship between use of all VGSC-inhibiting (anticonvulsant and Class I antiarrhythmic) drugs and overall survival of cancer patients. We will focus on carcinomas of the breast, colon and prostate because they are the most common and VGSC expression has been extensively studied in these tumours.[11 13-17 26-29]
- The relationship between use of all VGSC-inhibiting drugs and cancer specific survival.
- The relationship between individual VGSC-inhibiting drugs and overall survival.

There are no systematic reviews exploring this area and we are addressing this gap by conducting a review concurrent to this study [PROSPERO registration number CRD42014013574].

## METHODS AND ANALYSIS

### Data source and sample selection

This study will use general practice data accessed from QResearch (http://www.qresearch.org), a large consolidated database derived from the anonymised health records of over 13 million patients from 753 general practices (representing around 7% of UK practices). QResearch data are collected from the EMIS GP computer system and have been validated using other sources and shown to yield similar results to other databases, e.g. the Clinical Practice Research Datalink (CPRD).[30 31] QResearch has been used previously to study associations between cancer and prescription information.[30]

An open cohort of 100,000 patients (aged 30 years or older) with a diagnosis of breast, colorectal or prostate cancer will be identified who were registered with a QResearch practice during the study period between 1st January 1998 and 31st December 2013. This will include all those cancer patients in the database who have a prescription of one of the index drugs recorded before their date of cancer diagnosis (Table 1).[32] The remaining patients will be randomly selected controls. Time from date of diagnosis to death will be investigated and data will be right-censored in patients who are still alive at the end of the study period. Cancer diagnoses will be based on Read code information (available online at clinicalcodes.org/medcodes/article/17/).

| Table 1. Voltage-gated $Na^+$ channel-inhibiting drugs | | | |
|---|---|---|---|
| Drug/derivative | Alternative names | Classification | British National Formulary (BNF) section[32] |
| Carbamazapine, eslicarbazepine, oxcarbazepine | Arbil, Carbagen SR, Epimaz, Inovelon, Tegretol, Teril, Timonil, Trileptal, Zebinix | Anticonvulsant | 4.2.3, 4.7.3, 4.8.1 |
| Disopyramide | Dirythmin, Isomide, Rythmodan | Class Ia antiarrhythmic | 2.3.2 |
| Flecainide | Tambocor | Class Ic antiarrhythmic | 2.3.2 |
| Lacosamide | Vimpat | Anticonvulsant | 4.8.1 |
| Lamotrigine | Lamictal | Anticonvulsant | 4.8.1 |
| Lidocaine | Lignocaine, Xylocard | Class Ib antiarrhythmic | 2.3.2, 15.2 |
| Mexiletine | Mexitil | Class Ib antiarrhythmic | 2.3.2 |
| Moracizine | Ethmozine | Class Ic antiarrhythmic | - |
| Phenytoin, fosphenytoin | Epanutin, Pentran | Anticonvulsant, Class Ib antiarrhythmic | 4.7.3, 4.8.1, 4.8.2 |
| Procainamide | Pronestyl | Class Ia antiarrhythmic | 2.3.2 |
| Propafenone | Arythmol | Class Ic | 2.3.2 |

| | | | |
|---|---|---|---|
| | | antiarrhythmic | |
| Quinidine | Kiditard | Class Ia antiarrhythmic | - |
| Ranolazine | Ranexa | Antianginal | 2.6.3 |
| Riluzole | Rilutek | Treatment for amyotrophic lateral sclerosis | 4.9.3 |
| Tocainide | Tonocard | Class Ib antiarrhythmic | - |
| Topiramate | Topamax | Anticonvulsant | 4.7.4, 4.8.1 |
| Valproic acid, sodium valproate | Convulex, Depakote, Epilim, Epival, Episenta, Orlept | Anticonvulsant | 4.2.3, 4.7.4, 4.8.1 |

**Exclusions**

Temporary residents and patients registered with QResearch within 12 months of data extraction will be excluded. Cases without diagnosis of one of the three index cancers (breast, colorectal, or prostate cancer) will be excluded. Patients with anomalous, incorrect or infeasible dates will be excluded, e.g., dates of cancer diagnoses recorded before birth or after death. We shall assume that dates of birth and death are correct. Any patient with a date of diagnosis that indicates they were younger than 25 at the time of diagnosis will be excluded as it is unlikely a person of that age would get one of these three cancers.

**Exposure**

A participant will be considered as exposed if they have had at least one prescription for one of the index drugs. Assuming continuous treatment use between prescriptions, we will identify two exposure groups: a *low* exposure group (less than 6 months worth of prescriptions) and a *moderate to high* exposure group (six months or more prescriptions). The exposed groups, separately and in combination, will be compared with the control group (cases without any prescription for one of the index drugs). Patients with one prescription for a drug that would have been used as a local anaesthetic, e.g. lidocaine, will be excluded.

**Outcome measures**

Metastasis is estimated to be responsible for 90% of deaths from solid tumours.[33] However, metastasis itself is not reliably recorded in GP data and so the primary outcome measure will be overall survival following cancer diagnosis as a proxy for metastasis. Secondary outcome measures will be cancer-specific survival for each index type of cancer and overall survival across each drug, numbers permitting.

**Confounding factors**

Data on the following confounders will be requested: age, gender, alcohol consumption, smoking status, body mass index (BMI) and ethnicity. Data on alcohol, smoking and BMI are routinely collected and as such a single patient may have multiple recorded observations for these variables assessed over time. We will consider the observations measured at the closest date before the date of cancer diagnosis, based on appropriate Read codes (available online at clinicalcodes.org/medcodes/article/17/). The patients will be categorised as follows:

- Alcohol consumption[34] categorised as: Non/trivial drinker (<1unit/day), Light drinker (1-2units/day), Moderate-very heavy drinker(3+units/day) and Not recorded/known.
- Smoking status[35] categorised as: Ex-smoker, Smoker, Non-smoker, and Not recorded/known.
- BMI,[36] categorised as Underweight (<18.5), Normal range [18.5-25), Overweight [25, 30), Obese (30+) and Not recorded/known.
- Ethnicity[37] categorised according to the groupings used in the 2011 UK census: White; Mixed/Multiple ethnic groups; Asian/Asian British; Black/African/Caribbean/Black British; Other Ethnic group. We shall also include a 'Not recorded/known' category.

**Sample size calculation**

Up to 100,000 eligible cases will be used, which is the maximum sample size that will be released by QResearch. At breast cancer diagnosis, approximately 6% of patients present with metastatic lesions, with bone being the most common site.[38] Of patients presenting without bone metastasis at diagnosis, 3.6% subsequently develop metastases.[39 40] The majority (90%) of metastases will lead to death.[33] Pharmacological blockade of VGSCs inhibits invasion of breast, colorectal and prostate cancer cells *in vitro* by 25-50%.[13 15 22 23] Therefore, assuming 3.6% of cancer diagnoses lead to a metastasis and most of these to death, with standard significance level alpha = 5% and power = 90%, we would require 4248 in the exposed group to detect a fall of 25% in the metastasis (or death) rate and 928 to detect a fall of 50%. This is based on 20 comparison patients per exposed patient, but this ratio is not critical. If we include 6% with a metastasis present at initial diagnosis, these numbers fall to 1503 and 330.

The prevalence of epilepsy is estimated to be 1%.[41] Together, the most commonly used VGSC-inhibiting anticonvulsants, phenytoin, lamotrigine, carbamazepine and valproate, account for >82% of all antiepileptic drug use.[42] By contrast, Class I antiarrhythmic drug use has been considerably less common: <5% in patients with cardiac arrhythmia.[43] Thus, using these data as a guide, we might reasonably anticipate that around 0.8% of cancer patients would be using one of these VGSC-inhibiting drugs. To meet our largest target sample size, 4248, we would therefore be looking for a sample that contained 530,000 people with a diagnosis of one of the target cancers. To meet the lower target of 928, we would require 116,000 diagnoses. Given that we are studying deaths rather than metastases *per se*, we will be unable to distinguish between metastases present at diagnosis and detected subsequently. Therefore, if we include 6% assumed to have a metastasis present at initial diagnosis, we would require 187,875 and 41,250 diagnoses to detect falls in metastasis of 25% and 50% respectively.

According to Cancer Research UK,[44] the lifetime risk in 2010 for the four major cancer sites was almost 13% (female breast), 6% (female lung), 8% (male lung), 6% (female bowel including anus), 7% (male bowel including anus) and 13% (prostate). Hence for our chosen sites, we expect approximately 21% of women and 20% of men to experience a positive diagnosis at some time. We will not have lifetime data for many in the database, but we might anticipate that 10% of a database sample would have a history of one of these sites. Thus the Qresearch database of 13 million people is large enough to achieve our largest sample target.

**Statistical analysis**

Analysis will be conducted in Stata v13, using two-sided significance at the 5% level. For each Cox model, only the patients with complete data for each of the covariates controlled for in the model will be included in the analysis.

***Descriptive summaries***

The characteristics of the comparison groups will be described using summary statistics. Categorical data will be presented as frequency and percentage, and continuous variables will be summarised using descriptive statistics (mean, standard deviation, median, 1st and 3rd quartiles, minimum and maximum). The flow of patients in the QResearch database will be presented in a diagram.

***Primary analysis***

The primary analysis will compare the combined exposure group to the control group. For each group, the distribution of time from diagnosis of cancer to death will be described using Kaplan-Meier survival estimates. Kaplan-Meier survival curves will be presented for the two groups. The statistical equivalence of the two curves will be tested using the log-rank test. Right censoring will occur if the patient is still alive at the end of the study period (31st December 2013). Median time to death, with a 95% confidence interval (CI) will be presented. If the estimated survivor function is greater than 0.5 throughout the study it will not be possible to estimate the median survival time and other percentiles survival values (i.e. 90%, 80%, 75%, as appropriate) will be presented.

We will compare the survival of exposed cases with control cases from time of diagnosis of one of the three index cancers using a Cox Proportional Hazards regression model. The endpoint will be all cause mortality. We will adjust the Cox

model for type of cancer (breast, bowel or prostate), gender and age at diagnosis. Age will be included with both a linear and quadratic term (age + age$^2$). We will assume that all included patients are receiving the most appropriate standard treatment for their disease, so we will not adjust for cancer-treating drug intake. Hazard ratios will be presented with p-values and 95% confidence intervals.

Cox regression assumes that the proportional hazards model applies. To assess this, we shall plot –log(-log(S(t))) against log(time), where S(t) is the survivor function at time *t*. The curves for the two groups should be parallel. We will also consider a chi-squared test of the Schoenfeld residuals to assess the null hypothesis of no relationship between the hazards in each group. If the assumptions are not met, we shall try to investigate why this is.

***Sensitivity analysis***

We will repeat the primary analysis, but adjust the Cox model, in turn, for confounding variables: ethnicity, body mass index, smoking and alcohol consumption.

***Secondary analyses***

Each of the following secondary end points will be analysed like the primary outcome (unless indicated) with identical censoring strategy:

- If cancer type proves to be a significant predictor in the primary model then we will consider cancer specific survival
- Survival of Low exposure group compared with control group
- Survival of High exposure group compared with control group

- Survival of combined exposure group and control group with outcome of time to death from first diagnosis of any cancer, since some patients may have a diagnosis of another cancer before one of breast, bowel or prostate (a category for 'Other' will be included in the covariate for type of cancer)
- Survival of patients dependent on the main drug class that they are exposed to (numbers permitting).

## ETHICS AND DISSEMINATION

This protocol has been independently peer-reviewed by the QResearch Scientific Board. It has also been approved by the University of York Ethical Review Process. Only the authors will have access to the data during the study, in order to guarantee confidentiality of patient information. An article detailing the results of the study will be submitted for publication in an international peer-reviewed journal, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.[45] The full statistical analysis will be available from the authors after publication of the results.

## AUTHORS' CONTRIBUTIONS

WB had the original idea for this study. CF and WB wrote the draft of the manuscript. IW, FM and MB contributed to the development of the idea, the study design, and revised the manuscript. All authors approved the final submitted version of the manuscript.

## FUNDING STATEMENT

This work was supported by the Medical Research Council [Fellowship G1000508] and the Wellcome Trust [ref: 097829] through the Centre for Chronic Diseases and Disorders (C2D2) at the University of York.

## COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

## REFERENCES

1. Rugo HS. The importance of distant metastases in hormone-sensitive breast cancer. Breast 2008;**17 Suppl 1**:S3-8 doi: 10.1016/S0960-9776(08)70002-Xpublished Online First: Epub Date]|.
2. Suva LJ, Griffin RJ, Makhoul I. Mechanisms of bone metastases of breast cancer. Endocr. Relat. Cancer 2009;**16**(3):703-13 doi: 10.1677/ERC-09-0012published Online First: Epub Date]|.
3. Hille B. *Ionic channels of excitable membranes*. 2nd ed. Sunderland (Massachusetts): Sinauer Associates Inc., 1992.
4. Brackenbury WJ, Calhoun JD, Chen C, et al. Functional reciprocity between Na+ channel Nav1.6 and β1 subunits in the coordinated regulation of excitability and neurite outgrowth. Proc. Natl. Acad. Sci. U. S. A. 2010;**107**(5):2283-88
5. Brackenbury WJ, Yuan Y, O'Malley HA, Parent JM, Isom LL. Abnormal neuronal patterning occurs during early postnatal brain development of Scn1b-null mice and precedes hyperexcitability. Proc. Natl. Acad. Sci. U. S. A. 2013;**110**(3):1089-94 doi: 10.1073/pnas.1208767110published Online First: Epub Date]|.
6. Catterall WA. From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. Neuron 2000;**26**(1):13-25
7. Brackenbury WJ, Davis TH, Chen C, et al. Voltage-gated $Na^+$ channel β1 subunit-mediated neurite outgrowth requires fyn kinase and contributes to central nervous system development in vivo. J. Neurosci. 2008;**28**(12):3246-56
8. Clare JJ, Tate SN, Nobbs M, Romanos MA. Voltage-gated sodium channels as therapeutic targets. Drug Discov. Today 2000;**5**(11):506-20
9. Mantegazza M, Curia G, Biagini G, Ragsdale DS, Avoli M. Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. Lancet Neurol. 2010;**9**(4):413-24 doi: 10.1016/S1474-4422(10)70059-4published Online First: Epub Date]|.
10. Vaughan Williams EM. The relevance of cellular to clinical electrophysiology in classifying antiarrhythmic actions. J. Cardiovasc. Pharmacol. 1992;**20 Suppl 2**:S1-7
11. Brackenbury WJ. Voltage-gated sodium channels and metastatic disease. Channels (Austin) 2012;**6**(5):352-61 doi: 10.4161/chan.21910published Online First: Epub Date]|.
12. Brackenbury WJ, Djamgoz MB, Isom LL. An emerging role for voltage-gated Na+ channels in cellular migration: regulation of central nervous system

development and potentiation of invasive cancers. Neuroscientist 2008;**14**(6):571-83 doi: 10.1177/1073858408320293published Online First: Epub Date]|.
13. House CD, Vaske CJ, Schwartz A, et al. Voltage-gated Na+ channel SCN5A is a key regulator of a gene transcriptional network that controls colon cancer invasion. Cancer Res. 2010;**70**(17):6957-67 doi: 10.1158/0008-5472.CAN-10-1169published Online First: Epub Date]|.
14. Grimes JA, Fraser SP, Stephens GJ, et al. Differential expression of voltage-activated $Na^+$ currents in two prostatic tumour cell lines: contribution to invasiveness in vitro. FEBS Lett. 1995;**369**(2-3):290-4
15. Fraser SP, Diss JK, Chioni AM, et al. Voltage-gated sodium channel expression and potentiation of human breast cancer metastasis. Clin. Cancer. Res. 2005;**11**(15):5381-89 doi: 10.1158/1078-0432.CCR-05-0327published Online First: Epub Date]|.
16. Brackenbury WJ, Chioni AM, Diss JK, Djamgoz MB. The neonatal splice variant of Nav1.5 potentiates in vitro metastatic behaviour of MDA-MB-231 human breast cancer cells. Breast Cancer Res. Treat. 2007;**101**(2):149-60
17. Brackenbury WJ, Djamgoz MB. Activity-dependent regulation of voltage-gated $Na^+$ channel expression in Mat-LyLu rat prostate cancer cell line. J. Physiol. 2006;**573**(Pt 2):343-56 doi: 10.1113/jphysiol.2006.106906published Online First: Epub Date]|.
18. Brackenbury WJ, Djamgoz MB. Nerve growth factor enhances voltage-gated Na+ channel activity and Transwell migration in Mat-LyLu rat prostate cancer cell line. J. Cell. Physiol. 2007;**210**(3):602-8 doi: 10.1002/jcp.20846published Online First: Epub Date]|.
19. Nelson M, Millican-Slater R, Forrest LC, Brackenbury WJ. The sodium channel beta1 subunit mediates outgrowth of neurite-like processes on breast cancer cells and promotes tumour growth and metastasis. Int. J. Cancer 2014;**135**(10):2338-51 doi: 10.1002/ijc.28890published Online First: Epub Date]|.
20. Brackenbury WJ, Isom LL. Na Channel beta Subunits: Overachievers of the Ion Channel Family. Front. Pharmacol. 2011;**2**:53 doi: 10.3389/fphar.2011.00053published Online First: Epub Date]|.
21. Chioni AM, Brackenbury WJ, Calhoun JD, Isom LL, Djamgoz MB. A novel adhesion molecule in human breast cancer cells: voltage-gated Na+ channel beta1 subunit. Int. J. Biochem. Cell Biol. 2009;**41**(5):1216-27 doi: 10.1016/j.biocel.2008.11.001published Online First: Epub Date]|.
22. Fraser SP, Salvador V, Manning EA, et al. Contribution of functional voltage-gated $Na^+$ channel expression to cell behaviors involved in the metastatic cascade in rat prostate cancer: I. lateral motility. J. Cell. Physiol. 2003;**195**(3):479-87
23. Yang M, Kozminski DJ, Wold LA, et al. Therapeutic potential for phenytoin: targeting Na(v)1.5 sodium channels to reduce migration and invasion in metastatic breast cancer. Breast Cancer Res. Treat. 2012;**134**(2):603-15 doi: 10.1007/s10549-012-2102-9published Online First: Epub Date]|.
24. Brackenbury WJ, Isom LL. Voltage-gated Na+ channels: potential for beta subunits as therapeutic targets. Expert Opin. Ther. Targets 2008;**12**(9):1191-203 doi: 10.1517/14728222.12.9.1191published Online First: Epub Date]|.
25. Singh G, Driever PH, Sander JW. Cancer risk in people with epilepsy: the role of antiepileptic drugs. Brain 2005;**128**(Pt 1):7-17 doi: 10.1093/brain/awh363published Online First: Epub Date]|.
26. Brisson L, Driffort V, Benoist L, et al. NaV1.5 Na(+) channels allosterically regulate the NHE-1 exchanger and promote the activity of breast cancer cell invadopodia. J. Cell Sci. 2013;**126**(Pt 21):4835-42 doi: 10.1242/jcs.123901published Online First: Epub Date]|.

27. Grimes JA, Djamgoz MB. Electrophysiological characterization of voltage-gated Na(+) current expressed in the highly metastatic Mat-LyLu cell line of rat prostate cancer. J. Cell. Physiol. 1998;**175**(1):50-8
28. Gillet L, Roger S, Besson P, et al. Voltage-gated Sodium Channel Activity Promotes Cysteine Cathepsin-dependent Invasiveness and Colony Growth of Human Cancer Cells. J. Biol. Chem. 2009;**284**(13):8680-91 doi: M806891200 [pii] 10.1074/jbc.M806891200published Online First: Epub Date]|.
29. Ding Y, Brackenbury WJ, Onganer PU, et al. Epidermal growth factor upregulates motility of Mat-LyLu rat prostate cancer cells partially via voltage-gated $Na^+$ channel activity. J. Cell. Physiol. 2008;**215**(1):77-81 doi: 10.1002/jcp.21289published Online First: Epub Date]|.
30. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to bisphosphonates and risk of gastrointestinal cancers: series of nested case-control studies with QResearch and CPRD data. BMJ 2013;**346**:f114 doi: 10.1136/bmj.f114published Online First: Epub Date]|.
31. Reeves D, Springate DA, Ashcroft DM, et al. Can analyses of electronic patient records be independently and externally validated? The effect of statins on the mortality of patients with ischaemic heart disease: a cohort study with nested case-control analysis. BMJ Open 2014;**4**(4):e004952 doi: 10.1136/bmjopen-2014-004952published Online First: Epub Date]|.
32. *British National Formulary London*: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2013.
33. Gupta GP, Massague J. Cancer metastasis: building a framework. Cell 2006;**127**(4):679-95 doi: 10.1016/j.cell.2006.11.001published Online First: Epub Date]|.
34. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 44 Alcohol drinking, 1988.
35. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 83 Tobacco smoke and involuntary smoking, 2004.
36. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 2007;**335**(7630):1134 doi: 10.1136/bmj.39367.495995.AEpublished Online First: Epub Date]|.
37. National Cancer Intelligence Network and Cancer Research UK. Cancer Incidence and Survival by Major Ethnic Group, England 2002-2006., 2009.
38. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. Br. J. Cancer 1987;**55**(1):61-6
39. Yong M, Jensen AO, Jacobsen JB, Norgaard M, Fryzek JP, Sorensen HT. Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999-2007). Breast Cancer Res. Treat. 2011;**129**(2):495-503 doi: 10.1007/s10549-011-1475-5published Online First: Epub Date]|.
40. Jensen AO, Jacobsen JB, Norgaard M, Yong M, Fryzek JP, Sorensen HT. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. BMC Cancer 2011;**11**:29 doi: 10.1186/1471-2407-11-29published Online First: Epub Date]|.
41. Joint Epilepsy Council of the UK and Ireland. Epilepsy prevalence, incidence and other statistics. http://www.epilepsyscotland.org.uk/pdf/Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11_(3).pdf 2011
42. Nicholas JM, Ridsdale L, Richardson MP, Ashworth M, Gulliford MC. Trends in antiepileptic drug utilisation in UK primary care 1993-2008: cohort study using the General Practice Research Database. Seizure 2012;**21**(6):466-70 doi: 10.1016/j.seizure.2012.04.014published Online First: Epub Date]|.

43. Fang MC, Stafford RS, Ruskin JN, Singer DE. National trends in antiarrhythmic and antithrombotic medication use in atrial fibrillation. Arch. Intern. Med. 2004;**164**(1):55-60 doi: 10.1001/archinte.164.1.55published Online First: Epub Date]|.
44. Cancer Research UK. Lifetime risk of cancer. 2014. http://www.cancerresearchuk.org/cancer-info/cancerstats/incidence/risk/statistics-on-the-risk-of-developing-cancer - Lifetime5).
45. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;**335**(7624):806-8 doi: 10.1136/bmj.39335.541782.ADpublished Online First: Epub Date]|.