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ABSTRACT

With the increasing utilization of medications worldwide, coupled with the increasing availability of long-term data, there is a growing opportunity and need for robust studies evaluating drug-cancer associations. One methodology of importance in such studies is the application of lag times. In this review, we discuss the main reasons for using lag times. Namely, we discuss the typically long latency period of cancer concerning both tumor promoter and initiator effects and outline why cancer latency is a key consideration when choosing a lag time. We also discuss how the use of lag times can help reduce protopathic and detection bias. Finally, we present practical advice for implementing lag periods. In

general, we recommend that researchers consider the information that generated the hypothesis as well as clinical and biological knowledge to inform lag period selection. In addition, given that latency periods are usually unknown, we also advocate that researchers examine multiple lag periods in sensitivity analyses as well as duration analyses and flexible modeling approaches.

KEYWORDS

Cancer, neoplasms, latency, induction period, pharmacoepidemiology, lag time

INTRODUCTION

While drug-cancer associations may be identified from preclinical studies and randomized controlled trials (RCTs), preclinical studies do not necessarily translate to humans [1], and RCTs are usually too small and short to detect rare outcomes with long latency periods such as cancer [2,3]. As such, large, methodologically robust pharmacoepidemiologic studies with extended follow-up are needed to examine the potential carcinogenic effects of medications. One important methodological consideration for such studies is the application of lag times.

In cancer pharmacoepidemiology, with the application of a lag time cancer outcomes diagnosed shortly after drug initiation are not regarded as those occurring during "exposed person-time." Likewise, a period after drug discontinuation is considered person-time at risk, due to residual effects of drugs on cancer risk. Figures 1A and 1B outline hypothetical examples of the application of lag times in new-user, active comparator cohort, and case-control study designs, respectively. In duration or dose analyses, lags should also be considered. For example, suppose we apply a 1 year lag period, and "long-term use" is defined as having the equivalent of five years of use of a drug. In this setting a patient should

be classified as a 'non-long-term user' until one year after they reached the threshold for long-term use.

Lag times are useful in drug-cancer studies to address, i) cancer latency, ii) reverse causality, and iii) detection bias [3–6] Yet, the value of lag periods has received relatively limited attention in scientific literature. Moreover, the lack of consideration of latency and lag periods appears common in cancer pharmacoepidemiology, with a recent evaluation identifying that only 33% of all studies of glucose-lowering medications and cancer considered latency in their analyses [7]. Therefore, in this review, we provide an overview of the methodological challenges lag times address in cancer pharmacoepidemiology and recommendations for their application.

An overview of the methodological challenges that lag periods can address.

1. Cancer latency

Carcinogenesis is widely accepted to be a multistage biological process of cellular transformation, with mutational and epigenetic changes driving progression through key stages, including initiation, promotion, progression, invasion, and metastases [4]. A carcinogen can act at any stage of carcinogenesis. In general, it is believed to take many years from exposure to a causative agent to cancer development and subsequent clinical manifestation and diagnosis [8].

This period includes two distinct concepts, the induction and latent periods [9]. The induction period corresponds to the time from exposure to a component cause and disease initiation i.e. the time of malignant conversion, which for cancer often takes many years. Once cancer has reached malignant conversion and is irreversible in the absence of therapy, the distinct latent period begins. Thus the latent period refers to the period between malignant conversion and clinical manifestation or detection (**Figure 2**) [9]. In practice, it is often not

possible to distinguish between these periods; thus, when we consider cancer latency, we often refer to the time from exposure to cancer detection, which includes both the induction and the latent period. The combination of both the induction and the latent period has been labelled by Rothman as 'the empirical induction period' however throughout the scientific literature this is most commonly referred to as 'latency', and as such we will do so throughout this review [9,10].

Minimum length of cancer latency periods

Latency periods vary by type of carcinogen, cancer type, dose, duration, and timing of first exposure [3,9,11]. Usually for hypothesized exposures, including drug-cancer associations, the latency period is unknown [8]. Knowledge of cancer biology and latent periods for other non-pharmacological exposures may offer insights relevant to pharmacoepidemiology and help aid in our choice of lag period. In the 1970s, early literature concluded that the latent periods for most cancers were log-normally distributed [12]. Despite this, studies investigating minimum latency periods for specific cancers remain limited. Studies have suggested that the latency period for ovarian cancer is between 30-40 years [13–15]. For colorectal cancer, it is thought to take 5-10 years from initiation to adenoma development and 5-15 years from adenoma to invasive disease [16]. The long latency of colorectal cancer has been corroborated by studies of smoking and colorectal cancer risk, with associations observed among those with over three decades between tobacco cessation and colorectal cancer [17,18]. An example of cancer developing years after drug exposure includes adenocarcinoma of the vagina and cervix associated with in-utero exposure to diethylstilbestrol, a synthetic estrogen used until the 1970s to prevent miscarriage and other complications. These cancers mainly developed before the age of 20 years; however, studies suggest that risk remains elevated even after age 40 [19–21]. Other examples include the

apparent latency period of approximately 15-20 years for phenacetin-associated urinary tract cancers [22–25], while carcinogenic effects of hydrochlorothiazide on non-melanoma skin cancers seem to appear after approximately five years of use [26–30] and any potential protective effects of aspirin on advanced adenomas and colorectal cancer appear to emerge in the region of 5-10 years [31–34].

Nadler and Zurbenko applied a Weibull survival model to estimate the approximate length of time between biological initiation to cancer diagnosis for 44 cancer types [14]. Overall, over 35 of these cancer types were estimated to develop at least ten years before cancer diagnosis, ranging from 6.6 years to 57 years for solid tumors and 2.2 and 35.7 years for lymphoproliferative cancers, highlighting the wide variability across cancer types.

Indeed, while most cancers typically have long latency periods, there are some examples of more rapid cancer development following exposure, particularly for hematopoietic cancers, which appear to have much shorter induction periods [4,35]. Such variability can be observed from observations of cancer risk associated with ionizing radiation after the atomic bomb explosions of 1945 in Hiroshima and Nagasaki. The risk of solid cancer increased around 10 years after the bombing, remaining elevated, while an excess in leukemia cases was observed two years after the bombing, peaking at around eight years [36,37].

In the pharmacoepidemiology setting, similar observations have been made for certain drug-cancer associations. For example, immunosuppressive agents, such as azathioprine, cyclosporin, and OKT3, have been demonstrated to have carcinogenic properties. Evidence originated from investigations in organ transplantation, where increases in non-Hodgkin's lymphoma are observed as early as within one year of transplant receipt [38–41]. The carcinogenic effects of these agents are hypothesized to be mainly attributable to decreased immune surveillance of cancer cells or increased infections that cause cancer rather than

genotoxicity. Similarly, chemopreventative effects of tamoxifen and aromatase inhibitors on breast cancer may appear within 1-2 years (60–63). However, the number of known examples of such short latency periods for drug-cancer associations is small.

In summary, the evidence of cancer latency from various exposures highlights several important considerations for the application and selection of lag periods in drug-cancer studies:

- While the length of cancer latency periods varies between cancer types and is largely unknown, they are thought to be at least several years.
- Many chemical carcinogens lead to increases in cancer incidence after more than 10 years.
- Some examples exist for effects within both the moderate (1-10 years) and short (less than one year) time frames.
- It is expected that there should be a relationship between the time course of chemopreventative effects of drugs and the latency of cancer(s) being prevented.

Cancer initiators versus cancer promoters

Drug carcinogenic latency periods are often thought about in terms of cancer initiation or promotion. Initiators can be considered a cause of the first clone of neoplastic cells and are often thought to be genotoxic [8]. A promoter is a drug that accelerates the progression or growth of pre-malignant or sub-clinical disease [9,42]. Therefore, initiators are considered to have longer latency periods than promoters. As such, those drugs displaying carcinogenic effects in short time periods, such as imbalances in cancer appearing in RCTs (except for lymphoproliferative cancers), are likely acting as promoters. One example is the observed increases in keratoacanthoma and squamous cell carcinoma in melanoma patients treated with the BRAF kinase inhibitors vemurafenib and dabrafenib [43–45], which may

appear as early as 26 weeks [46]. It is hypothesized that BRAF inhibitors increase mitogen-activated protein kinase signaling in pre-malignant cells, promoting progression to detectable squamous cell carcinomas [45,46]. Other examples of tumor promoter effects are thought to include squamous cell carcinoma associated with immunosuppressant medications [47,48] and hormone replacement therapy and estrogen receptor-positive breast cancer [49,50]. A contemporary example includes the apparent association between pioglitazone and bladder cancer, where early imbalances were observed in trials [51,52], including the IRIS trial, which excluded patients with a history of bladder cancer and those at high risk (45). These findings were corroborated in several observational studies, indicating that potential increases in risk are observed within two years of use [53,54].

The evaluation of drug-cancer associations, particularly those with new medications that emerge from RCTs or case reports with short exposure periods, is complicated by the fact that often the mechanisms underlying cancer associations are unknown. Researchers may be too quick to dismiss associations observed within shorter periods of time as non-causal [55]. Indeed researchers should be mindful of falsely declaring a medication safe. Walker suggests that 'the observation is the hypothesis' and argues the appropriate response is to test the signal in a similar setting under controlled circumstances with sufficient statistical power [55]. However, it is difficult to draw conclusions in the absence of a biological model, as is often the case. Additionally, hypotheses of carcinogenesis also commonly arise from pharmacology and studies after drug approval. In general, while the information that generated the signal is important, so too is our understanding of cancer biology and latency to help inform assumptions. Overall, examples of tumor promotion effects are limited, and given the typically long latency of cancer, most cancer-drug associations are considered to have longer latency periods. Researchers need to draw on our existing biological knowledge

of the cancer of interest and acknowledge the uncertainty around the biological mechanisms of drug-cancer associations. In summary:

- Variability in latency of drug-cancer associations may be described in terms of drugs acting as initiators or promoters.
- Initiators generally have longer latency periods than promoters.
- Cancer promoter effects are less common, and the mechanisms underlying carcinogenic drug effects are often unknown.

Residual effects of drugs on cancer risk

Patients may remain at risk for a considerable time after treatment discontinuation. This can occur as patients accumulate exposure there is the accumulation of stochastic events, such as mutations caused by a drug, which may take some time to occur. After a threshold cumulative dose has been attained, there may be the appearance of a 'carry-over' effect even if the drug is subsequently discontinued. As such researchers may often lag exposure after discontinuation, whereby for a selected period after discontinuation of a given drug a study participant will be considered exposed. As observed in former smokers, for whom, although reductions in risk of lung cancer are observed upon quitting, increases remain for over 30 years after cessation [56]. In the pharmacoepidemiological setting, evidence suggests breast cancer risk declines but remains elevated for 10 years or more after stopping menopausal hormone therapy [57]. By contrast, studies have shown that the risk of breast cancer associated with oral contraceptive use disappears rapidly upon discontinuation [58–60]. However, it is suggested that it may persist for up to five years, depending on the previous duration of use [61,62]. Indeed, there is often a correlation between cumulative use and timing/recency of drug use, particularly for those medications taken for years. Those

exposed to higher cumulative doses must remain on the medications to accumulate such levels and are more likely recent users.

Most often, the relevant risk window after discontinuation is unknown. While evaluating the residual effects of drugs on cancer risk provides important information on the drug-cancer associations, in practice, this is often difficult due to limited follow-up in data sources. Considering the minimum lag periods required to observe an association (e.g., often 10 years or more), there is often insufficient follow-up time after treatment discontinuation to evaluate if risks decrease and subjects may meaningfully stay at risk indefinitely.

In summary:

- Drugs may have residual effects on cancer risk that remain long after drug discontinuation (e.g., 10 or more years).
- Alternatively, the elevated risk may disappear rapidly (less than one year) or within a moderate time from discontinuation (1-5 years); however, the length may be influenced by the previous duration of use.

2. Protopathic Bias

In addition to latency considerations, lag times also help mitigate protopathic bias (or reverse causation). Protopathic bias arises when a medication of interest is prescribed (or discontinued) for an early manifestation of an underlying disease of interest that has yet to be diagnosed [6,63]. This may incorrectly lead to the appearance of causal associations (reverse causality), resulting in an overestimation or underestimation of risk estimates. Protopathic bias is a particular problem for a symptomatic outcome that remains undiagnosed, as is often the case for cancer. In cancer pharmacoepidemiology, this phenomenon was described in the context of estrogen and endometrial cancer where,

estrogen was prescribed to treat uterine bleeding, a symptom of underlying endometrial cancer [64], for bladder and prostate cancer, and medications for overactive bladder, conditions that share symptoms [65,66] and for proton pump inhibitors and pancreatic cancer, with early symptoms misinterpreted as reflux [67]. Indeed, for the latter example, Table 1 outlines how lag periods can be applied and varied in sensitivity analyses. In this case-control study, odds ratios were elevated when removing the 2-year lag period in main analyses, with estimates returning to unity with a 6-month lag period, indicating elevations in odds of pancreatic cancer in the absence of a lag period was a result of reverse causality [67]. A previous Danish study investigating the new use of medications before cancer diagnosis generally found that the incidence of new drug use increased from around six months prior to a cancer diagnosis, although patterns varied considerably by cancer type [68]. In this study, increases in drug initiation close to cancer diagnosis were observed for drugs that may be indicated for symptoms of specific cancers, e.g., laxatives in colon cancer or inhaled medication in lung cancer, as well as in general across all cancers with treatments such as analgesics and antibiotics. While this suggests reverse causality may sometimes be eliminated with a lag of six months, there are notable examples where reverse causality is seen for more extended periods, such as up to two years for incretin-based medications for type 2 diabetes and pancreatic cancer [69].

3. **Detection bias**

Detection bias is a systematic difference in measurement or diagnosis of the outcome between exposure groups, which can occur through various mechanisms. Detection bias may be introduced if new users of a certain drug differ from those who do not initiate. For example, certain drug users, in particular those of preventative medications such as statins, may be more likely to engage in health-seeking behaviors including cancer screening

('healthy user bias'), which may lead to increased detection of cancers, in particular early stage cancer [70]. Alternatively, users of certain medications may be more likely to avoid screening [71]. Detection bias was also an issue widely discussed in the context of estrogen and endometrial cancer, as estrogen use is associated with bleeding, which may lead to increased screening for endometrial cancer, potentially leading to an overestimation of risk [72,73]. In another example, recent reports have investigated benign prostatic hyperplasia (BPH) and its treatments and the risk and progression of prostate cancer [74–77]. However, both conditions affect the same organ and cause voiding problems [74,78]. A recent study has highlighted higher total prescription rates of BPH medications in men with prostate cancer before diagnosis, in particular for new prescriptions initiated in the year prior to diagnosis [79]. Their findings suggest that some of the association between BPH, its treatments and prostate cancer may be influenced by increased diagnostic workup for prostate cancer in men with BPH, as well as reverse causality and surveillance bias. Interestingly, in the Danish utilization study outlined in the section above, increases in drug initiation close to cancer diagnosis were not only observed for drugs indicated for cancer symptoms but also non-cancer drugs such as antidiabetics [68]. This suggests that bias may also be introduced due to frequent interaction with physicians prior to a cancer diagnosis, leading to a diagnosis of an unrelated condition and initiation of new treatments or alternatively increased healthcare utilization around drug initiation leading to increases in detection. Surveillance bias may be introduced if there is increased scrutiny or contact with the healthcare system for one treatment group throughout the entire treatment period [80]. Of note, this differs from detection bias (increased detection around drug initiation) and is not dealt with by the application of lags or confounding control but rather by using a comparator group with similar surveillance patterns. Studies investigating diagnostic workup around drug initiation have found differential screening or diagnostic workup rates between drug users pre- or post-

initiation, e.g., differential breast mammography rates between metformin and sulfonylurea users [81,82]. This highlights that detection bias is not only problematic for non-user comparator groups but also in active comparator settings. One example is the elevations in breast cancer for up to four years of use of GLP-1 receptor agonists compared to DPP-4 inhibitors [83], appearing to be driven by weight loss effects of GLP-1 receptor agonists, with mammography and diagnostic workup rates higher among those experiencing greater weight loss [84]. The application of an appropriate lag period after drug initiation means cancer outcomes diagnosed shortly after drug initiation are not regarded as during exposed person-time, thus allowing a long enough period for undiagnosed cancer to become apparent, removing exposed events likely due to reverse causality or detection bias.

In summary;

- Reverse causality is introduced when an exposure of interest is prescribed or avoided due to signs or symptoms of undiagnosed cancer.
- Increased healthcare contact around cancer diagnosis may lead to the initiation of drug treatment, or increased healthcare utilization at treatment initiation may lead to increased cancer detection.
- Detection bias may also be introduced when drugs under study elicit side effects that increase cancer detection.

Challenges in the application of lag times in studies of drug-cancer associations

Given the complexities outlined above, defining the most appropriate lag time for a given study may not be straightforward and depends on the specific drug-cancer association being studied. The choice of lag time is an important design consideration as biologically misspecified lag periods may affect results. The long induction periods for drug cancer associations can have implications as exposure measured at different points along the

pathway e.g., during the latent period may result in exposure misclassification (information bias). When a period of exposure that is not etiologically relevant is included, estimates may be biased towards the null, with higher variance and decreased statistical power. In general relative risk estimates will increase as the lag is more correctly specified. However, when applying longer lag periods, it is important to remember that a lagged estimate might be confounded by disregarded exposure. For example, if we increase the lag time from two to five years, which leads to the risk estimate increasing, we may conclude the lag is more correctly specified. However, if the now disregarded exposure has a causal role, then the rate ratio is likely confounded upwards by disregarded exposure.

It is important to note that when concerns about the carcinogenic effects of drugs emerge from RCTs within relatively short timeframes, it may be relevant to apply a shorter lag period or remove the lag period altogether to replicate analyses so potential protopathic bias may be uncovered.

Data availability may also present challenges when applying biological meaningful lag periods. In certain instances, data sources may have limited follow-up, and applying a longer lag period may result in the exclusion of many patients from analyses. While this may pose a challenge to researchers, selecting a shorter lag period based solely on data availability could lead to misleading findings and should be avoided.

Limited studies have evaluated the methodological question of aiming to identify an optimal value for a lag time. Some have used cubic splines to model appropriate risk windows and lag periods [85,86]; however, these may be population-specific and not generalizable [3]. Other data-driven methods [68] also have limitations, including the assumption that estimates would move toward a plateau with increasing lag time and the failure to differentiate lag time effects and dose-response associations. The use of penalized distributed-lag nonlinear models has been proposed, but too requires unverifiable

assumptions about the nature of the lag-response [87,88]. An emerging area of development to account for the interaction between time since initiation and cumulative duration is the application of flexible weighted cumulative exposure methods, in which time-dependent exposure is weighted by recency of use [89,90]. In general, further methodological advances are warranted.

Other considerations: the interaction between lags and dose-response analyses

In addition to lagged analyses, duration/dose-response analyses are also of importance for the interpretation of drug-cancer associations. For most cancer associations, we do not expect the hazard function to be proportional over time, and averaged estimates may not give a meaningful representation of how risk varies over time [3]. Duration or dose-response analyses provide insight into the potential mechanisms of associations, identify potential biases, including reverse causality and detection bias, and point towards potential causality [91]. For example, while recent studies of phosphodiesterase inhibitors and melanoma have reported elevations in risk overall, associations with low-level exposure and the failure to observe a clear dose-response relation argue against a causal relationship [92]. The use of lags does involve dropping data and potentially useful information. The graphical representation of hazard functions over time using flexible modeling methods or stratifying on cumulative duration, dose, or time since initiation, using all available data (without a lag), are also very useful. For example, in a scenario where there is a two-year latency period, based on prior knowledge, we may assume *a priori* a biologically plausible lag period of two years and pre-specify time-varying exposure groups of 1-2 years, 2-5 years which are altered in sensitivity analyses. This method has the advantage of presenting all the data and allows

for evaluating reverse causality and detection bias, where associations may be observed within short duration categories, and for directly inspecting the potential latency period.

The importance of duration response analysis in understanding the mechanisms of associations raises questions on the usefulness of very long lag periods. If, for example, we were to apply a 10-year lag period, which may be biologically plausible based on prior knowledge of the latency period for the drug-cancer association under investigation, we may expect associations to diverge at day one, as the first 10 years of drug use are disregarded. This can make it more difficult to identify potential biases and the causal mechanism. Thus, we may decide to apply a lag period of <10 years so that these can be investigated. This however will mean, that with the inclusion of person-time that is not at risk, overall averaged estimates will be diluted [6], reflecting the impact of latency on duration response. Thus if using lag times shorter than what we expect to be biologically reasonable overall 'ever use' estimates should be avoided.

Recommendations

As outlined above, the typically long induction and latent period of most cancers, the potential for reverse causality, and detection bias justify the application of lags in drug-cancer studies. We make the below recommendations for researchers undertaking studies of drug-cancer associations.

1. In studies of drug-cancer associations, the relevant latency periods of cancer and the issues of reverse causality and detection bias should always be considered in the planning of the design and analyses, with methods, which may include lag periods, applied to investigate this. Results should be interpreted with these issues in mind.

2. Researchers should consider the information that generated the hypothesis/cancer signal and clinical and biological knowledge to help inform their assumptions of the relevant latency period. These should always be stated transparently and a priori.

3. Researchers should acknowledge uncertainty around a biologically meaningful lag period in sensitivity analyses and their interpretation of results [93]. Researchers are encouraged to consider a range of lag times in sensitivity analyses. Additionally, duration response analyses, viewing the hazard function over time using flexible modeling methods such as cubic splines, and using all data in sensitivity analyses are recommended.

LIST OF ABBREVIATIONS

BPH, Benign prostatic hyperplasia; DPP-4, Dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1 ; RCT, Randomized controlled trial

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FIGURE LEGENDS

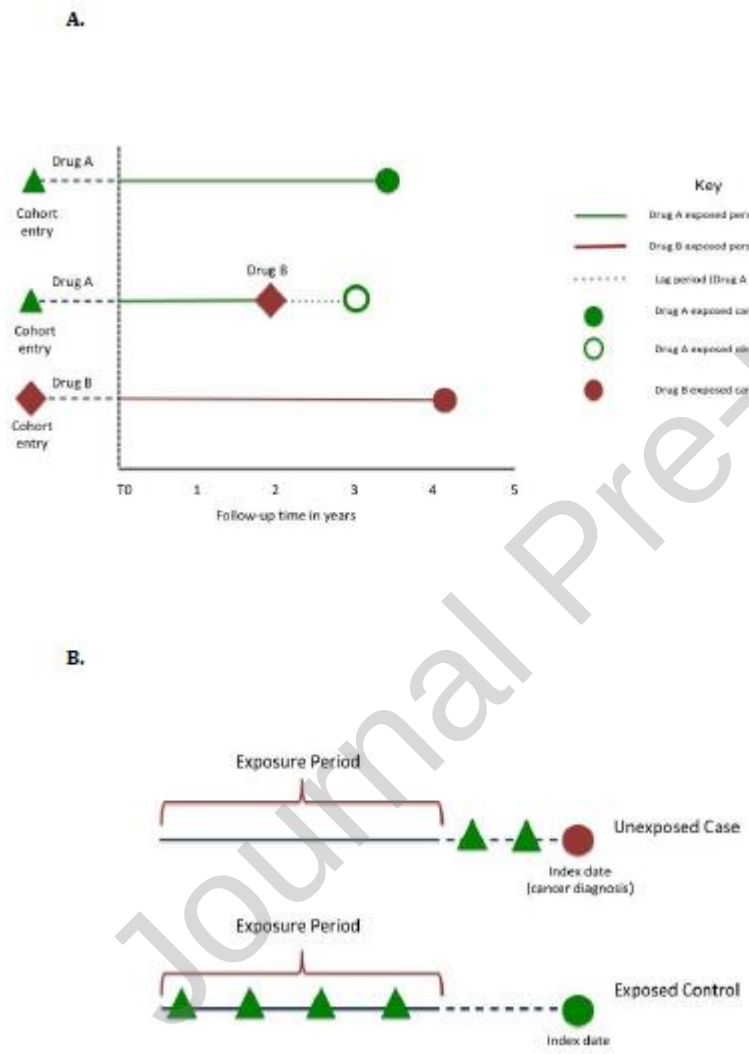

Figure 1A. Figure depicting the application of lag periods in a cohort setting.
Each line represents patients entering the cohort. All patients enter the cohort on their first prescription of either Drug A (the study drug) or Drug B. In this hypothetical example, there is a one-year latency period. As such we exclude those entering the cohort with less than one year of follow-up. Follow-up (T0) begins for all patients entering the cohort one year after their first prescription and patients are followed until a cancer diagnosis or other censoring criteria such as death, or one year after a switch between study drugs (accounting for a one-year lag period). This is outlined for example in Patient 2. Patient 2 enters the cohort on a prescription for drug A. They are followed up from one year after cohort entry, contributing exposed person time to Drug A, until one year after their switch to Drug B, at which point they are censored. In this hypothetical setting, we assume drug effects on cancer are

irreversible and remain after treatment discontinuation therefore patients are considered continuously exposed from cohort entry irrespective of discontinuation.

Figure 1B: Figure depicting the application of lag periods in a case-control study. In this figure, the dashed lines represent the lag period, during which prescriptions are disregarded. In the above example, the selected case receives prescriptions for Drug A only during the lag period, therefore is considered unexposed, while the control is considered exposed.

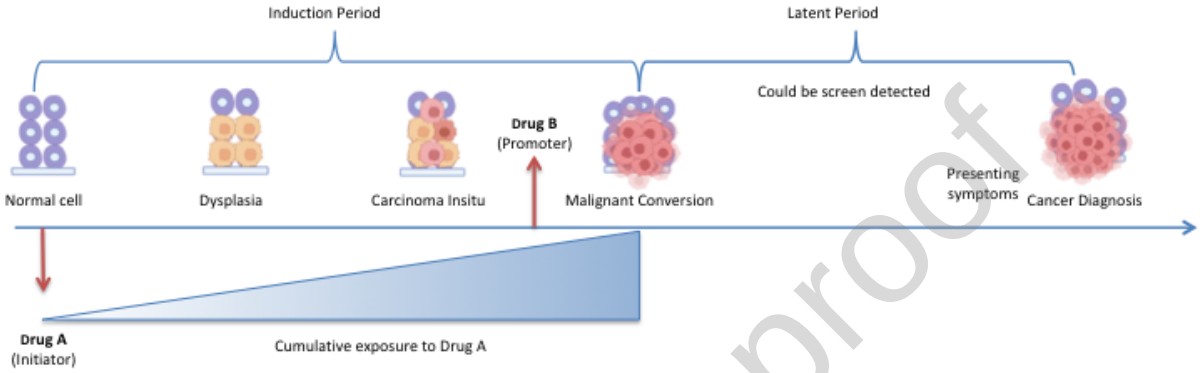

Figure 2: Figure outlining the intervals from normal tissue to cancer diagnosis. The induction period corresponds to the time between a component cause (Drug A) and the initiation or growth acceleration of a cancer. In the above, Drug A is a tumor initiator, that is the cause of the first clone of neoplastic cells. The latent period corresponds to the time between the irreversible malignant conversion (in the absence of treatment) from a non-malignant precursor to invasive cancer and clinical manifestations or detection. In the above, Drug B is acting as a tumor promoter, that is a drug that accelerates the progression or growth of pre-malignant or sub-clinical disease.

Table 1 Effects of varying exposure lag time on estimates of the association between high-use (≥1,000 DDDs) of PPIs and risk of pancreatic cancer in a case-control study.

Lag-time (months)	Adjusted OR (95% CI)[†]
0	1.51 (1.31-1.73)
6	1.02 (0.90-1.17)
12	1.00 (0.87-1.15)
18	0.97 (0.85-1.12)
24	0.92 (0.79-1.07)
30	0.92 (0.79-1.07)
36	0.94 (0.80-1.10)
42	0.97 (0.82-1.14)
48	0.95 (0.80-1.12)
54	0.96 (0.81-1.15)
60	0.97 (0.81-1.16)

Abbreviations: OR, odds ratio; CI, confidence interval.
†A lag-time of 24 months corresponded to the main analysis.
Adapted from Hicks *et al* Pharmacoepidemiol Drug Saf. 2018;27:926–930 [64].

Declaration of Competing Interest

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: