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Cancer pharmacoepidemiology symposium

Connections between pharmacoepidemiology and cancer biology: designing biologically relevant studies of cancer outcomes

The increasing utilization of prescription drugs among adults in the United States demonstrates the need to remain vigilant in evaluating the relationship between nononcologic medications and the development of cancer [1]. Pharmacoepidemiology is the study of the utilization, safety, and effects of medications in a population. Well-designed pharmacoepidemiology studies can examine the relationship between medication use and the risk of either initiating or promoting cancer. Within the context of pharmacoepidemiology studies commonly used to evaluate these associations, developing a comprehensive understanding of biological mechanisms and disease pathways can provide complementary knowledge toward hypothesis development, study design, methodology, and analysis to evaluate cancer as an adverse outcome. There are several types of available data sources for observational research including but not limited to administrative claims data, electronic health records, survey data, and disease registry data. A significant limitation of some of these data sources is that variables may not be collected for research and are typically ascertained for treatment or billing purposes. Commonly collected data elements vary by data source and can include demographic variables, medical diagnoses, medical procedures, and treatment-related details coded to standardized classifications or nomenclatures (ICD, Read, SNOMED-CT, HCPCS, CPT, NDC, RxNorm, MEDRA, LOINC, DRG). The following concepts aim to guide purposeful connections between biologic foundations and pharmacoepidemiology studies.

Cancer biology overview

Carcinogenesis is the multistage biological process of cellular transformation through initiation, promotion, progression, invasion, and metastasis. The transitions from one stage to the next are believed to correspond to mutational (germline and somatic) and epigenetic changes associated with cellular regulatory processes including tumor suppressor genes, oncogenes, and stability genes, as well as host factors like immune response. Table 1 provides an overview of selected terms to reference for a more robust understanding of cancer biology processes. Even a basic understanding of the complex pathways (such as TNF-NFκB or MAPK) or genomic alterations may stimulate the development of novel biologically driven research questions, and new hypotheses that can be examined in pharmacoepidemiology studies. The process of carcinogenesis is linked to a variety of etiologic factors (genotoxic and nongenotoxic carcinogens—defined in Table 1). Medications along with numerous other endogenous and exogenous sources comprise these factors and specific examples are shown in Figure 1. Careful examination of the biological influences in both the design and analysis phases is beneficial when assessing the relationship between medications and cancer risk.

Broad considerations for characterizing exposure

Understanding cancer biology may be useful in determining the risk window for exposure and the biological plausibility of an exposure association. Ascertaining the biologically relevant study period, which includes an exposure risk window, is both pivotal and challenging. The exposure risk window indicates the period of susceptibility to the effect of the exposure. It may vary on biological factors, for example, immune system development may be a time of particular vulnerability to carcinogenic effects. The effect of the exposure also varies based on a myriad of factors, such as drug type, duration of exposure, intensity of exposure, and other measured and unmeasured covariates as well as varying by cancer type.

Biological plausibility suggests that there could be a potential mechanism for carcinogenesis. For example, with an immunomodulatory agent (e.g., anti-TNF drugs), it would be logical to look at cancers which are specifically related to immune regulation such as T cell and B cell lymphomas [2]. Similarly, if a drug alters estrogen or progestin levels, one strategy could be to investigate whether the drug is potentially related to a hormonally induced or promoted cancer such as the case with hormone replacement therapy and the development of breast cancer [3]. The Woman's Health Initiative provides a clear example. The Woman's Health Initiative study showed hormone replacement therapy (HRT) may increase the risk of estrogen receptor-positive breast cancer. Subsequent to this finding, a significant drop in HRT prescriptions was observed in 2002. A decrease in breast cancer incidence followed from 2002 to 2005 but only among estrogen receptor-positive tumors [4]. The timing of HRT exposure (postmenopausal) and subsequent results suggests that the outcome may be related to cancer promotion rather than initiation, as breast cancer takes time to clinically manifest. Thus, determining the relevant exposure risk window for studies of hormonal agents with similar estrogenic pathways should consider the potential influence of biology on the relevant risk window of exposure while also ensuring selection of the biologically appropriate population of interest (e.g., postmenopausal women).

Even taking into account these biological concepts and developing a strong biologically driven study design, supplementary methods may uncover additional insights. Uncertainties in calculating a biologically relevant exposure risk window favor the application of sensitivity analysis to examine the effects of varying drug exposure periods on the risk of outcomes. Modeling these

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Table 1
Selected cancer biology terms

Terminology	Definition
Carcinogenesis	The complex interplay between genetics, environmental exposure, and external factors which induces conditions that are conducive to the development and progression of cancer. The steps of carcinogenesis initiation, promotion, and progression (invasion, metastasis).
Driver gene mutation	Mutation that confers a selective growth advantage.
Epigenetic	Changes unrelated to DNA sequencing that affect gene expression or phenotype.
Genotoxic	Agents that induce direct DNA damage in their carcinogenic action.
Germline	In the genome from conception, inherited. Example: A germline mutation is inherited.
Nongenotoxic	Agents that induce cancer, but not directly through DNA damage such as through tumor promotion, endocrine modification, immune suppression, tissue-specific toxicity, and inflammatory responses.
Oncogene	Proto-oncogenes normally function in the promotion of cell growth and cell division, however mutations cause uncontrolled division from usual upregulation mechanisms which force dominant or gain-of-function mutations. Activation of these genes to oncogenes is linked to cancer.
Passenger gene mutation	Mutation that has no effect on neoplastic process and occurs during general proliferation (successive clonal expansions). These mutations account for >99.9% of the alterations in tumors.
Somatic	In a non-germ cell, is not inherited. Example: A somatic mutation is not inherited.
Tumor suppressor gene	Normal function of tumor suppressor genes is to prevent or suppress cancer by keeping cell division regulated, which maintains the system to avoid cancer by down regulation of cell proliferation. However, loss-of-function mutations force inactivation of these mechanisms. Inactivation of these genes is linked to cancer.

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alternative windows to define exposure attempts to demarcate important periods of exposure contribution and account for biological factors fundamental to the association. The results of testing these assumptions may allow for assessment of observed and unmeasured confounding [5]. In particular, selecting the appropriate exposure definition can minimize measurement biases such as misclassification, which is essential for strong internal validity. The use of sensitivity analysis may also be useful when scientific questions have limited previous research or unknown biological mechanisms, relying on related clinical or methodological knowledge for study design.

Quantifying drug exposure

Alongside identification and definition of exposure lies the principle of appropriate measurement of an exposure. The dose-response relationship is one pharmacologically relevant basis for beginning to assess various adverse events associated with medication use. Exposure (dose) can be evaluated in a myriad of ways such as medication strength, cumulative therapeutic duration, defined daily dose, area under the concentration time curve (AUC), calculation of adherence (MPR or PDC), or calculation of relative dose intensity (commonly used for chemotherapy). Dose measures

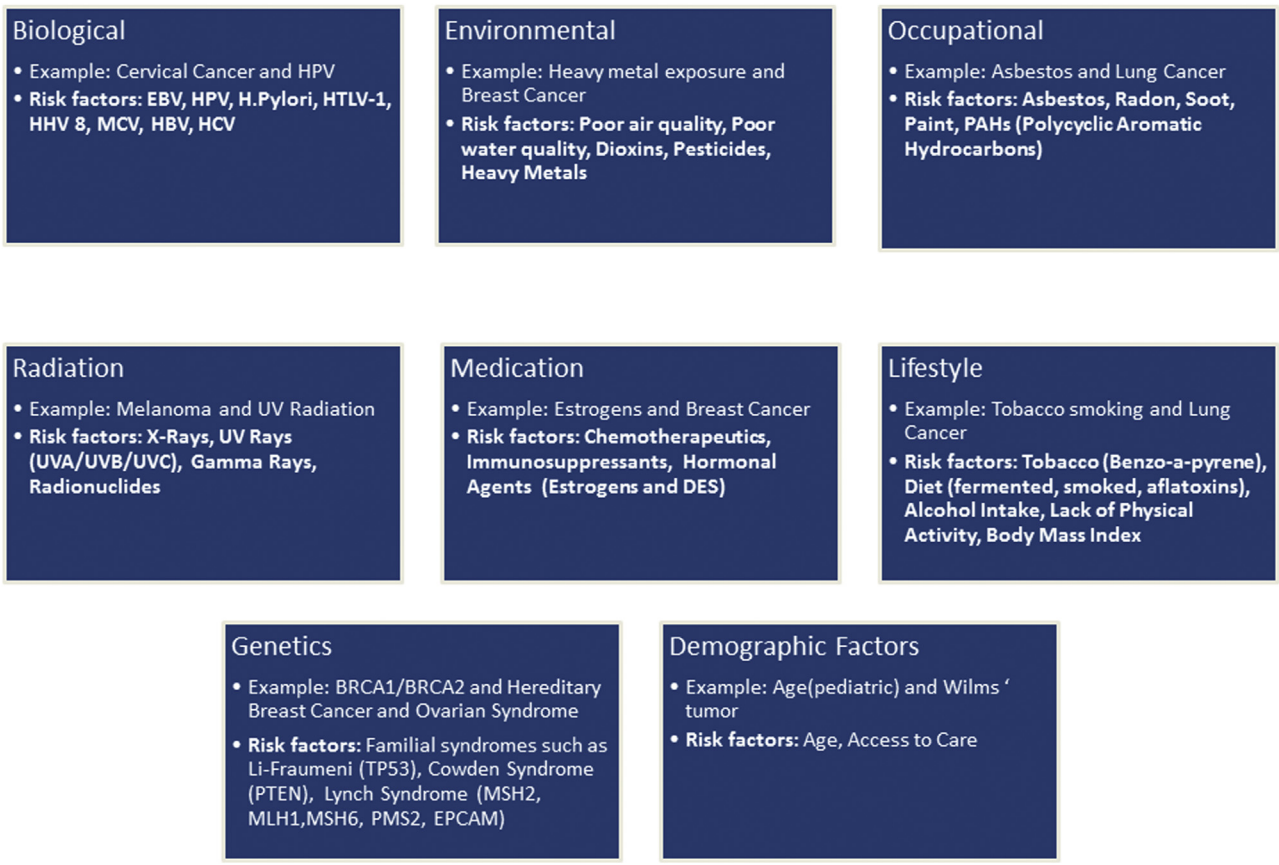

Fig. 1. Examples of potential etiologic causes of cancer.