Risk Factors

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H. Comber
National Cancer Registry, Cork, Ireland

In epidemiology, a **risk factor**, or ***exposure***, is an event, condition or characteristic which modifies the risk of an event or ***outcome***. The relationship between exposure and outcome is the effect of the exposure.

Why Should Oncologists Worry About Risk Factors?

When a patient has been diagnosed with cancer, the risk factors that caused it might not be of great importance to the oncologist who is treating her. However, it is still important to know about the types of study that investigate risk factors, not least because improved survival and life expectancy of cancer patients have led to an increase in the risk of second cancers (Oeffinger et al, 2013), partly due to treatment effects (Kamran et al, 2016; Morton et al, 2014) and partly due to the risk factors that were responsible for the first cancer (Berrington de Gonzalez et al, 2011). Addressing behavioural risk factors may reduce subsequent risk for the patient (Khuri et al, 2001) and family members may also seek information on reducing their cancer risk (Bottorff et al, 2015; Howell et al, 2013; Radecki Breitkopf et al, 2014). Furthermore, all physicians have a responsibility to give advice that might prevent ill health, and to be aware of the strengths and limitations of the evidence supporting this advice.

Measurement of Risk

Risk is defined as the number of events divided by the number of people at risk. When measured over a specified period of time, it is described as the **incidence rate**. Differences in risk due to an exposure may be expressed as a ratio or a difference.

Risk	Number of events/number of people at risk
Risk ratio	Risk of exposed/risk of unexposed
	▪ measures the strength of the effect
	▪ is independent of the population risk
Risk difference	Risk of exposed - risk of unexposed
	▪ describes the number of additional cases due to the exposure
Excess or **attributable risk** (Parkin, 2011; Whiteman et al, 2015)	
	▪ is the difference in the risk of a condition between an exposed population and an unexposed population

Risk ratio and risk difference

In a study of hormone replacement therapy (HRT) (Jones et al, 2016), 500 out of 20 114 non-users and 52 out of 1612 users of combined HRT developed breast cancer (Table 1). The risk to users was 3.6% and to non-users 2.5%, giving a risk ratio of 1.30 (i.e. the risk to users was 30% greater). The difference in risk was 0.74%, equivalent to 12 (1612 × 0.74%) additional cases of cancer in the 1612 users.

Table 1 *Relative Risk of Postmenopausal Breast Cancer, by Type of HRT Preparation*
From Jones ME, Schoemaker MJ, Wright L, et al. Menopausal hormone therapy and breast cancer: what is the true size of the increased risk? Br J Cancer 2016; 115:607-615.

	All women	Cases	Risk (%)
Non-users	20 114	500	500/20 114=2.5%
Oestrogen/progestogen HRT	1612	52	52/1612=3.2%
Risk ratio (3.2%/2.5%)			1.30
Risk difference (3.2%–2.5%)			0.74%

Causation

Risk factor epidemiology tries to separate the effects of the exposure being investigated from all other exposures. This is important because cancer may develop following a series of different exposures over a long period, so the identification of all possible exposures is challenging.

Establishing Causation

Study conditions in epidemiology are difficult to control, so a single study is rarely definitive, and evidence of causation depends on accumulated evidence. Interpretation of this evidence may be controversial.

Mobile phones and brain cancer

The INTERPHONE (INTERPHONE Study Group, 2010) and other large studies (Benson et al, 2013) have produced strong evidence that there is no association between mobile phone use and brain cancer, but controversy continues concerning a range of methodological issues (Lagorio and Röösli, 2014; Morgan et al, 2015).

The epidemiologist Bradford Hill (Hill, 1965) proposed certain aspects of a study which suggest causation (Table 2).

Table 2 *Bradford Hill's Criteria for Causation*

- Strength: An exposure which increases the risk of the outcome by 5% is less convincing than one which doubles it
- Consistency: Has the association been repeatedly observed in different places, circumstances and times?
- Specificity: Is the association limited to particular sites and types of disease?
- Temporality: Does the exposure precede the outcome?
- Biological gradient: Does the association show a dose–response curve?
- Plausibility: Is the causation biologically plausible?
- Coherence: This is related to plausibility – does the effect cohere with the generally known facts of the natural history and biology of the disease?
- Experiment: If some preventive action is taken, does it in fact prevent the outcome?
- Analogy: Has a similar exposure been shown to be associated with a similar outcome?

Study Design

Cancer risk factors are often suggested by observing variation in cancer incidence or **mortality** between populations differentiated by geography, time, occupation or other characteristics. **Hypotheses** developed from these observations are tested in analytical studies. These are typically **cohort** or **case-control studies**, but sometimes a **randomised trial** (see Chapter 6) might be used.

Types of Epidemiological Study

Table 3 *Advantages and Disadvantages of Different Study Types*

Study type	Advantages	Disadvantages
Cohort study	Clear sequence of events Risk can be measured Low risk of selection bias	Large numbers of participants needed with long follow-up period, so expensive and often slow New exposures difficult to add Loss to follow-up Change in exposure status during study Risk of confounding
Randomised trial	Clear sequence of events Risk can be measured Low risk of bias or confounding	Large numbers of participants needed with long follow-up period, so expensive and often slow New exposures difficult to add Loss to follow-up Change in exposure status during study Ethical issues
Case-control study	Relatively small number of participants needed Disease objectively confirmed No follow-up period needed; no drop-outs	Risk cannot be calculated Prone to selection bias, recall bias and confounding Limit to exposures studied Difficult to acquire biological samples

Cohort studies

A cohort is a group of people followed over a period, some of whom will have the exposure of interest and some of whom will have the outcome of interest. Participants are assessed for many exposures in addition to that under investigation and often have biological samples taken. For rare exposures, it is necessary to find cohorts with a high **prevalence** of exposure, such as occupational groups (Kachuri et al, 2016), while general population cohorts are used for more common exposures (Riboli, 2001). A randomised trial can be thought of as a type of cohort study where the exposure is randomly assigned by the researcher. **Field trials** are the custom in cancer epidemiology, where participants in the community are randomised, either individually or by group (e.g. by area of residence or clinic attended).

The Gambia Hepatitis Intervention Study (The Gambia Hepatitis Study Group, 1987)

The Gambia Hepatitis Intervention Study is a large-scale study of the prevention of liver cancer by hepatitis B (HBV) vaccination of young infants. The latest estimates (Viviani et al, 2008) indicate that the number of cases needed to detect a significant difference between vaccinated and unvaccinated groups will be reached when subjects are around 30 years old, between 2017 and 2020.

Case-control studies

Case-control studies begin with identified cases of cancer whose exposures are compared to those of a group of people without cancer (controls). Both groups are drawn from the same **source population**. The source population may be patients attending a hospital or clinic, the population of a region or other defined population. The **control group** is chosen at random from this source population. Sometimes, cases and controls are drawn from an existing cohort. This would be a **nested case-control study** which provides better quality information on exposures.

Sources of Error in Risk Factor Studies

The errors which occur in studies of causation are of two kinds: systematic and random.

- **Systematic error** is unaffected by study size
- **Random error** decreases with increasing study size

Systematic error

Systematic errors are divided into bias and confounding.

- **Bias** can be considered as an error in the conduct of a study (**selection bias**, measurement bias)
- **Confounding** is an error in study design or interpretation of study results

Bias

Selection bias. Selection bias occurs when the exposed and unexposed populations differ in ways (other than the exposure) which affect the outcome. Selection bias can give rise to the 'healthy worker' effect, where the effect of an occupational exposure is countered by the overall better health of those in active work (Zielinski et al, 2009). Selection bias may also occur if participants volunteer for the study for reasons related to the exposure, e.g. interest in a healthy lifestyle.

Bias is difficult to avoid in the selection of the controls for case-control studies. They may be chosen from patients with non-cancer conditions attending the same hospital or from people living in the same area or attending the same family doctor, and so may have risk factors in common with cases.

Measurement bias. Exposure measurement: Bias in recall of self-reported exposures is common in case-control studies. Bias may be **differential** between cases and controls, as patients with cancer are more likely to recall a specific exposure, or it may be **non-differential**, due to under-reporting of factors such as alcohol and tobacco intake. Differential bias may lead to over- or under-estimation of the effect, but non-differential bias will always lead to under-estimation. Where possible, self-reported exposures should be independently validated.

Outcome measurement: Bias in outcome measurement is uncommon in cancer epidemiology, although cancer diagnoses may be missed in cohorts for which the **follow-up** is inefficient. Overdiagnosis, or earlier diagnosis, may occur in cohorts where the exposed participants are more intensively monitored.

Confounding

Confounding is a common source of error in interpretation. A confounder is something which affects the outcome but not the exposure of interest, and is correlated with the exposure. For instance, heavy drinkers tend to smoke, which means that high alcohol consumption is associated with, but does not cause, lung cancer. Smoking is therefore a confounder of

the relationship between alcohol and lung cancer. Confounding occurs frequently in cancer studies, due to the large number of potential carcinogenic exposures. While bias can be minimised by adherence to good study design and practice, minimising confounding requires a thorough knowledge, measurement and analysis of potential exposures and is usually part of study analysis as well as design.

Random Error

The relation between exposure and outcome is unpredictable at the individual level, and measures of effect in individuals will be randomly distributed around some best estimate (e.g. an average). The usual measure for showing the scatter around the estimate is the 95% **confidence interval**. There are various interpretations of this interval, but in practice it is used to test if the data are consistent with some hypothesis (see also Chapter 8). Random error reduces with study size but can also be reduced by study design and conduct and by having a homogeneous study population.

Statistical Testing

Statistical testing determines how consistent the measured effect is with a hypothesised effect (see Chapter 8). The hypothesis is usually that there is no effect, or that there is no difference between two effects (**null hypothesis**). Conventionally, if the 95% confidence intervals of the measured effect do not overlap those associated with the null hypothesis, it is considered that there is a real effect. Confidence intervals are more informative than probabilities (**p-values**) which give little information about the underlying data.

Risk ratios and **odds ratios** are conventionally presented as unadjusted and adjusted. The **unadjusted ratio** is the simple risk ratio or odds ratio (risk exposed/risk unexposed). On the other hand, an **adjusted ratio** arises from statistical models which allow for the effects of other variables and confounders (e.g. age, sex, smoking, body mass index) which may affect the risk. Table 4 shows an example of unadjusted and adjusted ratios and their confidence intervals.

Table 4 *Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals for Colorectal Cancer Risk Associated With Duration of Observed Insulin Exposure*
From Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology 2004; 127:1044-1050. Copyright © 2004. Reprinted with permission from the American Gastroenterological Association.

	Cases	Controls	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)*
No insulin therapy (reference)	107 (83.6)	1084 (87.5)	1.0	1.0
≥5 years of insulin use	4 (3.1)	15 (1.2)	2.8 (0.9–8.5)	4.7 (1.3–16.7)

*Adjusted for sex and 7 other variables.

Interpretation

How important is the effect? Two factors determine the clinical importance of an effect:

- The size of the effect
- The frequency of occurrence of the exposure

Large effects, even with wide confidence intervals, should not be ignored if they fulfil criteria of plausibility. Small, **statistically significant** effects are common in large studies, but may be artefactual. However, small effects with high exposure prevalence may have public health importance. Where the background risk is low, risk difference is more informative than risk ratio, because the risk ratio may exaggerate the importance of an effect. The **STROBE** (Strengthening the Reporting of Observational Studies in Epidemiology) initiative has produced a detailed guide on the reporting and interpretation of **observational studies** (Vandenbroucke et al, 2007), which describes how these studies should be reported.

Representativeness

Studies of cancer risk factors are investigations of aetiology, which are presumed to have a biological basis. Although there may be differences in susceptibility between populations, the effects of risk factors are usually similar in all populations. Good study design is therefore more important (Doll et al, 2004) than the issue of whether the participants are representative of the wider population.

Publication Bias

Many initial studies of risk are small and poorly designed. If they test a novel hypothesis, they are less likely to be published if they fail to support this hypothesis. If published, they are likely to be followed by larger studies, which are more likely to be published. Small negative studies of risk tend to be under-reported, leading to bias in reviews and **meta-analysis**. Figure 1(a) shows the **forest plot** of a meta-analysis (see Chapter 9) of the risk of prostate cancer in first-degree relatives of prostate cancer patients (Bruner et al, 2003). Figure 1(b) shows a **funnel plot** of the same data. The vertical dashed line indicates the weighted average, around which individual studies should be symmetrically grouped. The smaller studies (at the bottom) are skewed to the right, suggesting that smaller negative studies were less likely to be published, causing **publication bias**.

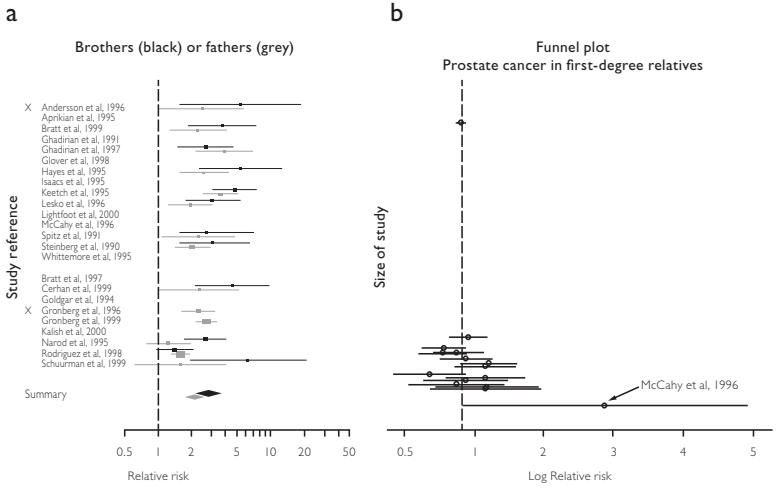

Figure 1 *(a) Relative risks of prostate cancer in men with a history of prostate cancer in a first-degree relative. (b) Funnel plot for first-degree relatives. The circles represent the estimates of the log relative risk for each study and the horizontal lines are 95% confidence intervals.*

From Bruner DW, Moore D, Parlanti A, et al. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. Int J Cancer 2003; 107:797-803. By permission of John Wiley and Sons.

Conclusions

While the European Code Against Cancer (International Agency for Research on Cancer, 2017) has only 12 proven recommendations for action to reduce risk, a PubMed search for 'cancer prevention/risk factors' yields over 130 000 citations. This prompts the question: how, and why, should a busy clinician deal with all this evidence? It is tempting to wait for consensus to be summarised in **systematic reviews** and meta-analyses (see Chapter 8). However, these vary in quality, may not be up to date and should not be regarded as a substitute for critical reading of key reference papers. Guidelines and checklists help in making an assessment of the evidence, but it is also important to assess the practical importance of the findings. Many 'positive' reports turn out to have little practical impact in the real world. It is the responsibility of all cancer clinicians to give cancer prevention advice, but to be aware of the strengths and limitations of the evidence.

Declaration of Interest:

Dr Comber has reported no conflict of interest.

Further Reading

Coggen D, Rose G, Barker DJP. Chapter 1: What is epidemiology? Epidemiology for the uninitiated, 4th edition. http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated/ (23 January 2018, date last accessed)

Dos Santos Silva I. Cancer epidemiology: principles and methods. https://www.iarc.fr/en/publications/pdfs-online/epi/cancerepi/CancerEpi.pdf.

Rothman K. Epidemiology—An Introduction, 2nd edition. London: Oxford University Press, 2012 (23 January 2018, date last accessed).

Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 2007; 4:e297.

References

Benson VS, Pirie K, Schüz J, et al. Mobile phone use and risk of brain neoplasms and other cancers: prospective study. Int J Epidemiol 2013; 42:792–802.

Berrington de Gonzalez A, Curtis RE, Kry SF, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol 2011; 12:353–360.

Bottorff JL, Robinson CA, Sarbit G, et al. A motivational, gender-sensitive smoking cessation resource for family members of patients with lung cancer. Oncol Nurs Forum 2015; 42:363–370.

Bruner DW, Moore D, Parlanti A, et al. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. Int J Cancer 2003; 107:797–803.

Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004; 328:1519.

Hardell L, Carlberg M, Söderqvist F, Mild KH. Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use. Int J Oncol 2013; 43:1833–1845.

Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965; 58:295–300.

Howell LA, Brockman TA, Sinicrope PS, et al. Receptivity and preferences in cancer risk reduction lifestyle programs: a survey of colorectal cancer family members. J Behav Health 2013; 2:279–290.

International Agency for Research on Cancer, European Commission. European Code Against Cancer. Available from: http://cancer-code-europe.iarc.fr (24 January 2018, date last accessed).

INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol 2010; 39:675–694.

Jones ME, Schoemaker MJ, Wright L, et al. Menopausal hormone therapy and breast cancer: what is the true size of the increased risk? Br J Cancer 2016; 115:607–615.

Kachuri L, Villeneuve PJ, Parent MÉ, et al, Canadian Cancer Registries Epidemiology Research Group. Workplace exposure to diesel and gasoline engine exhausts and the risk of colorectal cancer in Canadian men. Environ Health 2016; 15:4.

Kamran SC, Berrington de Gonzalez A, Ng A, et al. Therapeutic radiation and the potential risk of second malignancies. Cancer 2016; 122:1809–1821.

Khuri FR, Kim ES, Lee JJ, et al. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial. Cancer Epidemiol Biomarkers Prev 2001; 10:823–829.

Lagorio S, Röösli M. Mobile phone use and risk of intracranial tumors: a consistency analysis. Bioelectromagnetics 2014; 35:79–90.

Morgan LL, Miller AB, Sasco A, Davis DL. Mobile phone radiation causes brain tumors and should be classified as a probable human carcinogen (2A) (Review). Int J Oncol 2015; 46:1865–1871.
Morton LM, Onel K, Curtis RE, et al. The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. Am Soc Clin Oncol Educ Book 2014; e57–e67.
Oeffinger KC, Baxi SS, Novetsky Friedman D, Moskowitz CS. Solid tumor second primary neoplasms: who is at risk, what can we do? Semin Oncol 2013; 40:676–689.
Parkin DM. 1. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer 2011; 105 Suppl 2:S2–S5.
Radecki Breitkopf C, Asiedu GB, Egginton J, et al. An investigation of the colorectal cancer experience and receptivity to family-based cancer prevention programs. Support Care Cancer 2014; 22:2517–2525.
Riboli E. The European Prospective Investigation into Cancer and Nutrition (EPIC): plans and progress. J Nutr 2001; 131:170S–175S.
The Gambia Hepatitis Study Group. The Gambia Hepatitis Intervention Study. Cancer Res 1987; 47:5782–5787.
Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLOS Med 2007; 4:e297.
Viviani S, Carrieri P, Bah E, et al. 20 years into the Gambia Hepatitis Intervention Study: assessment of initial hypotheses and prospects for evaluation of protective effectiveness against liver cancer. Cancer Epidemiol Biomarkers 2008; 17:3216–3223.
Whiteman DC, Webb PM, Green AC, et al. Cancers in Australia in 2010 attributable to modifiable factors: summary and conclusions. Aust N Z J Public Health 2015; 39:477–484.
Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology 2004; 127:1044–1050.
Zielinski JM, Garner MJ, Band PR, et al. Health outcomes of low-dose ionizing radiation exposure among medical workers: a cohort study of the Canadian national dose registry of radiation workers. Int J Occup Med Environ Health 2009; 22:149–156.