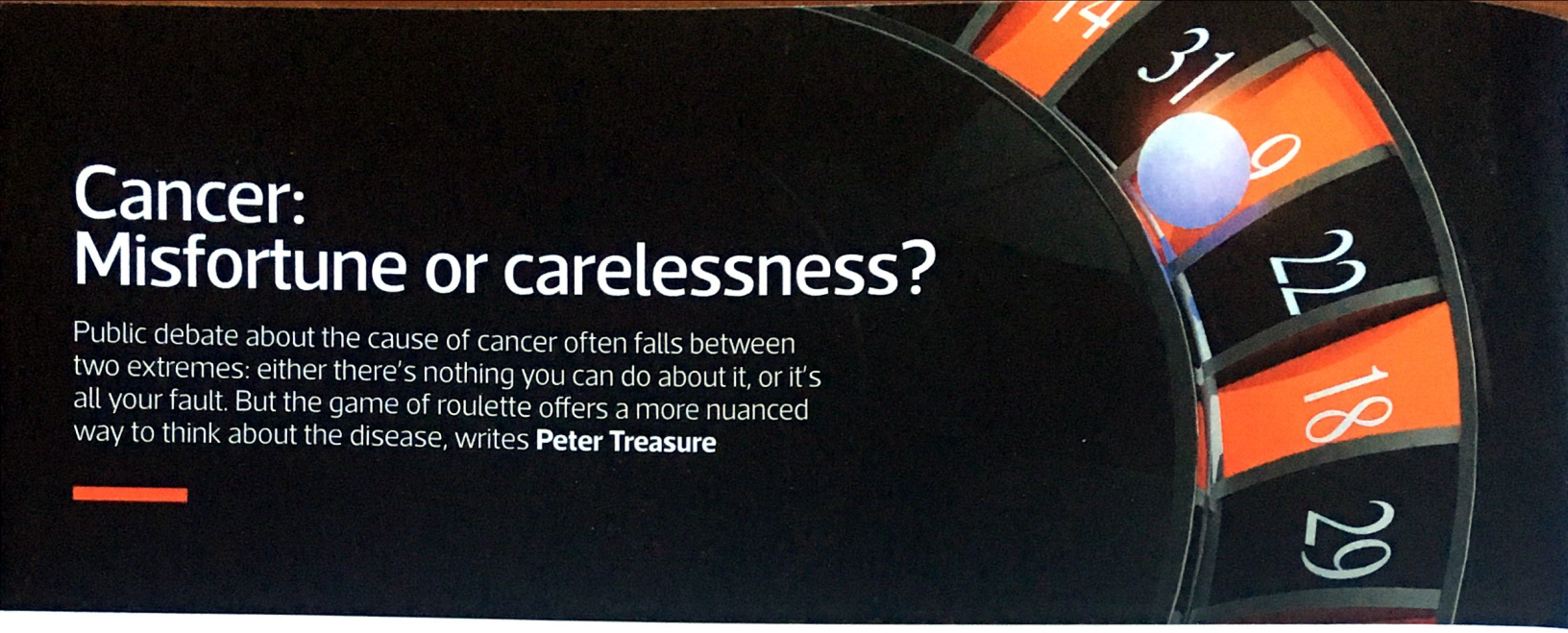

Cancer: Misfortune or carelessness?

Public debate about the cause of cancer often falls between two extremes: either there's nothing you can do about it, or it's all your fault. But the game of roulette offers a more nuanced way to think about the disease, writes **Peter Treasure**

The world is a complicated place. We must necessarily, personally and professionally, deal with simplified versions of it: models or analogies. No matter how simple our models are, they must be realistic enough to be useful, and realistic models often incorporate random processes. But humans are notoriously poor at understanding randomness, as is evidenced in recent public discussions of the "causes" of cancer.

The extremes of the positions presented are: that developing cancer is entirely a matter of luck ("nothing you can do about it") or entirely determined by lifestyle choices such as poor diet or a negative attitude ("all your fault").

A realistic model will represent a synthesis of the extremes, recognising both the role of chance and how these chances can be influenced by genetics, environment and lifestyle.

How we think about health, the models we unconsciously construct and analogies we are comfortable with, has direct consequences for our future well-being. For example, a smoker who thinks his lungs are good for 100 000 cigarettes before irreversible damage occurs is less likely to give up smoking than one who thinks each individual cigarette might cause a mutation which leads to lung cancer. Likewise, perceiving a glass of red wine as "concentrated sunshine" has different consequences than viewing it as a flavoured solution of the poison, ethyl alcohol.

Tomasetti and Vogelstein (T&V) published a paper in 2015,[1] with a follow-up in 2017,[2] which has resulted in considerable controversy. They demonstrated that the lifetime risk of cancer for a particular body tissue is strongly associated with the lifetime number of stem cell divisions in that tissue, a phenomenon over which we have no control. The take-home message of the popular media from this finding was that cancer is entirely a matter of chance, with the implication that individuals have no influence on their fate. T&V's paper was, of course, much more nuanced (even though the accompanying press release was headlined "'Bad luck' of random mutations plays predominant role in cancer, study shows" (bit.ly/2xAOXT8)).

Then, in April 2015, Lucas and Sapiro (L&S) wrote a thought-provoking discussion in *Significance* of the T&V paper, asking: "Cancer: What's luck got to do with it?"[3] They describe the popular interpretation of that paper – "cancer develops randomly and [therefore] healthy living *makes little difference*" – as "catastrophic and pessimistic".

The media present a "random event" as an event which cannot be influenced. But readers of this magazine will know otherwise, theoretically and empirically. In the case of cancer, there is a mountain of evidence showing that lifestyle and environment influence risk – despite the underlying random events. We need therefore a model of cancer where the possibility of influence is built in: that is, "cancer develops randomly, but healthy living *makes a difference*".

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The car

The most concrete way to communicate a model to the general public is to construct an analogy. In a subsequent discussion, T&V provided an analogy to aid interpretation of their paper: "Getting cancer could be compared to getting into a car accident." The car accident analogy is based on the length of the trip corresponding to the number of stem cell divisions and the accident corresponding to the diagnosis of cancer, there being a high correlation between the length of the trip and the risk of an accident. The mechanical condition of the car corresponds to the inherited genetic factors, road conditions correspond to the environment, and driving style corresponds to lifestyle.

L&S did not find this analogy very helpful. It does not provide a natural way to think about how randomness is modified by genes, environment and lifestyle. T&V in fact end up making opaque statements, such as: "Using this analogy, we would estimate that two-thirds of the risk of getting into an accident is attributable to the length of the trip."

Another analogy recently proposed (bit.ly/2wEatd9) is that of a vase falling off a shelf: the destruction of the vase being due to the fall corresponds to the diagnosis of the cancer being due to random mutations during cell division, with the initial push corresponding to other factors. Again, this analogy does not adequately incorporate the role of chance.

The roulette wheel

A more useful analogy would be one which embeds a random process but permits, in a natural way, the inclusion of genetic, environmental and lifestyle influences. I would like to propose instead a roulette-based analogy. Randomness is fundamental to the development of cancer, and randomness is fundamental to the spinning of a roulette wheel. Genetic, environmental and lifestyle influences can be incorporated easily. And, importantly, repeated spins of the wheel mimic the passage of time.

The imaginary roulette wheel has numbered pockets about its circumference, say one thousand in total. Initially, we assume that some small number of distinct "bad" events – five, say – are necessary to occur in the right order before a particular kind of cancer develops: a "bad event" may be, for example, a mutation arising in a stem cell division. This process is represented by a person's roulette wheel being spun each day and, with each event corresponding to the ball ending up in a particular numbered pocket, the diagnosis of cancer corresponds to the five numbers coming up in the right order. (See model 0 in the accompanying box.)

This analogy captures the randomness and the development with time. But the assumption of each bad event having the same probability is completely unrealistic. The next step in our modelling is to give the different bad events different probabilities. This is easily done by defining a bad event not as a single pocket of the wheel, but as a set of pockets (model 1).

We now have an adequate analogy for an individual. We capture the differences between individuals by varying the number of pockets corresponding to each bad event (and perhaps even changing the number of events required). If a lifestyle choice increases the probability of a particular cancer, that could be represented by a larger set of bad pockets for a particular event (model 1a) – and if a person makes a beneficial change to their lifestyle, some pockets stop being bad. A congenital genetic mutation may mean that the second bad event need not occur at all (model 1b).

Despite their crudeness and lack of realism, such models provide a context in which we can see that external factors such as genes, environment and lifestyle can influence purely random processes. A very basic quantitative model can replace conceptual obscurity with straightforward mechanisms.

I do not suggest that such a model can practicably be constructed for any particular cancer. Instead, I am presenting a generic analogy for the development of cancer: the random process being central, with a natural representation of the passage of time, mechanisms for permitting genetic, environmental and lifestyle influences and – most importantly – the means for capturing changes in lifestyle. ■

The carcinogenesis roulette analogy

Model 0

Imagine a roulette wheel with a thousand numbered pockets about its circumference. Each spin of the roulette wheel corresponds to a new day. Certain pockets, at certain times, represent a "bad" event. Five bad events in a defined order are needed for a particular cancer. An example would be:

{610} → {238} → {165} → {168} → {693}

which indicates that the first bad event occurs the first time the ball lands on 610, the second when it lands on 238 after the first bad event occurs, and so on, up to malignancy occurring when the ball lands on 693 after the fourth bad event.

Model 1

It is unrealistic for all bad events to have the same probability, so the model is revised such that a bad event may also occur if the ball settles in one of several pockets. The example is now:

{610} → {238} → {165 or 166} → {multiple of 42} → {693}

In this example the probability per spin of the third bad event is twice that of the first two events, and the fourth bad event has an even higher probability.

The model can now be enhanced to recognise that the definition of a bad event may be characteristic of the individual person.

Model 1a

Suppose, for example, that a lifestyle choice is known to hasten markedly the development of a cancer. The required sequence of events could look like:

{610} → {238} → {165} → *If lifestyle = Y then* {multiple of 2} *otherwise* {multiple of 42} → {693}

where *Y* symbolises a detrimental behaviour such as smoking. Note that if a person changes their lifestyle for better (or worse), then the roulette wheel changes such that the number of bad pockets decreases (or increases).

Model 1b

Similarly, if a congenital genetic mutation *Z* means that the second bad event need not occur, then the sequence of events can be pictured as:

{610} → *If congenital mutation Z is present then* omit 2nd event *otherwise* {238} → {165} → {multiple of 42} → {693}

Note

Readers may be reminded of the Armitage–Doll multistage model. Any numbers presented have been chosen arbitrarily for illustrative purposes and bear no relationship to any actual cancer.

References

1. Tomasetti, C. and Vogelstein, B. (2015) Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*, **347**(6217), 78–81.

2. Tomasetti, C., Li, L. and Vogelstein, B. (2017) Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science*, **355**(6331), 1330–1334.

3. Lucas, J. E. and Sapiro, G. (2015) Cancer: What's luck got to do with it? *Significance*, **12**(2), 40–42.