

Chapter 2

The Behavioural Dimension of Cancer and Sickness

Animals behave in specific manners when they are sick, and some of those behaviours may be adaptive responses to disease, whereas others may be a more straightforward result of dysfunction. Conversely, behaviours such as stressful social interactions may affect the normal functioning of the organism contributing—alone or in conjunction with other factors—to disease development. We start this chapter by reviewing the biological aspects of the interface between behaviour and disease in animals, with special reference to cancer in humans, to then explore in more detail the relationship of human cancer with pain, fatigue, sleep disorders, nausea and the various senses.

Behaviour of Sick Animals

For a long time the behaviour of sick animals was considered an unremarkable subject of study. If an animal is debilitated by an infectious pathogen or a disease such as cancer, then it is no wonder that it may lack the energy to function and behave normally, leading, in the most extreme of cases, to loss of tissue mass and fluids that could ultimately result in death. This view was challenged by Neal Miller in the 1960s with his research on the sickness behaviour of animals injected with subseptic doses of endotoxin. Miller concluded that sickness behaviour is a result of an adaptive motivational state rather than an effect of physical debilitation (Miller 1964). The theme was further developed in the late 1980s by Benjamin L. Hart in his seminal work published in *Neuroscience and Biobehavioral Reviews*. There, Hart (1988: 123) formulated “the perspective that the behavior of sick animals and people is not a maladaptive response or the effect of debilitation, but rather an organized, evolved behavioral strategy” released by disease. The concept that fever in particular is an evolutionarily adaptive response to disease had also been developed by Matt Kluger in the 1970s (Kluger 1978). Of course, sickness behaviour can take extreme, even pathological, forms (Dantzer 2009), in which case the organism may indeed be

Table 2.1 Sickness behaviours

Hypomotility (lethargy)
Asthenia (lack of energy)
Hyperthermia (fever)
Hypophagia (anorexia)
Adipsia (reduced drinking)
Hyperalgesia (increased sensitivity to pain)
Anhedonia (incapacity to experience pleasure)
Hypersomnia (increased time spent sleeping)
Emotional depression
Decreased interest in exploration
Decreased interest in social activities
Decreased sexual activity
Lack of grooming activity
Disruption of memory
Shortness of breath

Modified from Table 2 of Dunn et al. (2005); see also Fig. 2.1 for some additional behaviours

suffering from a deterioration of health; but in its more common manifestations, the set of behaviours associated with a sick state is a result of an evolved adaptation against some of the damaging effects of disease.

Sick animals and humans in particular tend to be lethargic in movements, behaviourally depressed, physically anorexic (that is, they lose body mass) and febrile. Such *sickness syndrome* is also accompanied by behaviours such as sleepiness, emotional depression, loss of appetite (hypophagia), reduction of drinking (adipsia), increased sensitivity to pain and lack of grooming, sexual activity and social interest among others (Hart 1988; Aubert 1999; Wagner et al. 2006; Dantzer 2009) (see Table 2.1). The sickness syndrome results from a re-organisation of the motivational priorities of the individual experiencing a drop in its usual healthy condition (Aubert 1999). Such re-organisation includes saving energy whilst also activating the immune system. That is, a sick animal will respond adaptively by shifting its usual physiological processes of homeostasis and associated behavioural repertoire to a mode that will allow it to better cope with the challenges imposed by disease. This has been shown experimentally in rats for instance, where sick animals kept under good housing conditions have been observed to interrupt behaviours typically associated with sickness, once confronted with an urgent priority such as retrieving scattered pups and improving insulation of the nest at lowered temperatures. Sickness behaviour is resumed once those urgent priorities have been attended to (Aubert 1999). That is, sickness behaviour is not necessarily evidence of an intrinsic debilitation of the organism but of a temporal rearrangement of the organism's physiological priorities.

Animals, including humans, affected by cancer may also manifest some or all of the behaviours that characterise the sickness syndrome (Cleeland et al. 2003, see also Kelley et al. 2003; Menéndez et al. 2003). That such behaviours can be adaptive is suggested, for instance, by the association of restriction of food ingestion,

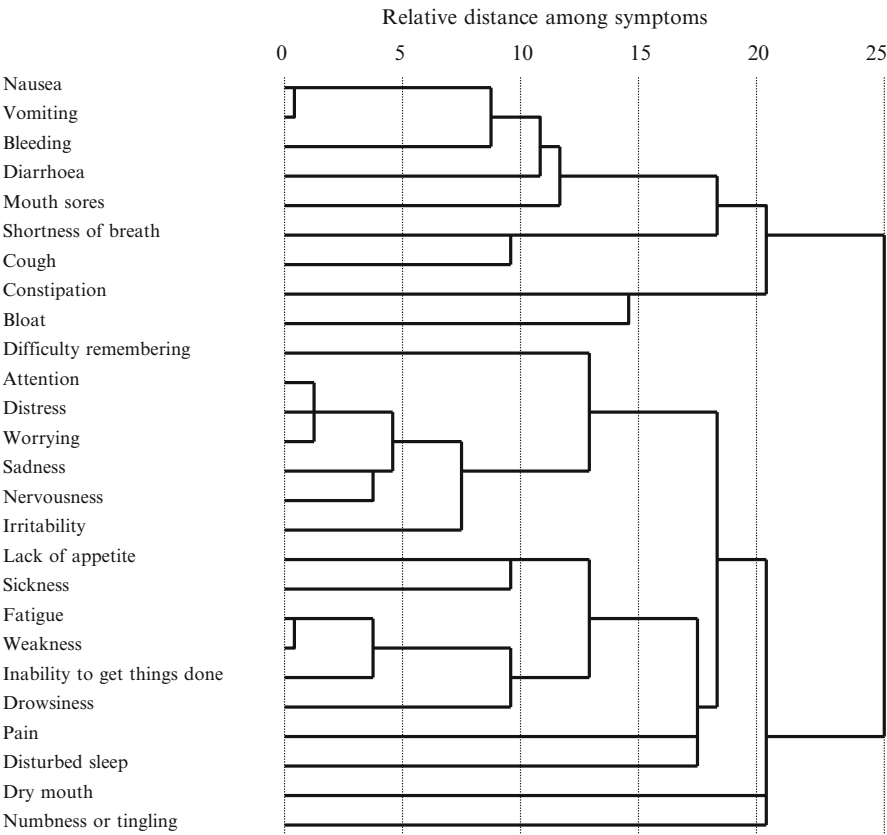


Fig. 2.1 Clustering patterns of cancer symptoms and effects of cancer treatment. Symptoms that cluster earlier (closer to 0) indicate co-occurrence as reported by patients (modified from Lee et al. 2004b; Cleeland et al. 2000)

following loss of appetite, with apoptosis (programmed cell death), at least in the liver, apoptosis being one of the defence mechanisms against cancer development (Konsman and Dantzer 2001). By ingesting less food the individual may promote death among cells of some organs, and such increased cell death rate may be useful whenever one or more of those organs are developing cancer. More broadly, if the sickness syndrome is an adaptive response then concurrent groups of symptoms should be observed, perhaps reflecting a coordinated reaction of the organism against the disease. Indeed, recent cluster analyses have shown that groups of symptoms co-occur during cancer (Cleeland et al. 2000, see review in Lee et al. 2004b), as shown in Fig. 2.1, symptoms that patients identify as co-occurring cluster earlier in the dendrogram. Thus affective and cognitive symptoms occur together, and they are more closely co-occurring with fatigue-related symptoms than with symptoms associated with gastrointestinal and respiratory system activity. In addition, it will be noted that symptoms of pain and sleep disturbance occur more or less

independently of the other symptoms (Lee et al. 2004a). Although the occurrence of symptoms in clusters may follow from specific causal adaptive links, this cannot be completely elucidated by a cluster analysis alone. To establish adaptive causation more specific empirical research is required. In particular, it is important to distinguish between those symptoms caused by the disease itself and those caused by treatment. The two clusters that include fatigue in one case and distress in the other are especially important as targets of research due to the high frequency in which these two symptoms occur in cancer patients. These considerations aside, disease may eventually develop to such an extent that symptoms do become evidence of actual damage to the organism rather than an adaptive response.

The mechanisms that cause the sickness syndrome involve immune, endocrine and nervous system components interacting in very specific manners that are slowly being unravelled (see van der Pompe et al.'s 1994 review for the case of breast cancer). We devote the rest of this section to reviewing some of those major mechanisms. In doing so, we endeavour to provide a somewhat detailed account of the mechanisms involved, as they are currently understood. Such level of detail is necessary in order to establish a firm causal link between behaviour, disease and health that will be subsequently used to evaluate the various associations between cancer and behaviour discussed in the rest of this and the other chapters.

Disease and the Neuro-Immune-Endocrine System

Given the central role of immunity in health and disease, let us start with the immunological aspects of the response to disease. Two major categories of organs form the immune system: (a) the *primary lymphoid organs* such as the bone marrow and the thymus, where cells of the immune system such as the monocytes, natural killer cells, polymorphonuclear granulocytes and T lymphocytes complete their maturation, and (b) the *secondary lymphoid organs* such as the lymph glands, mucus-associated lymphoid tissue and spleen, where antigens or foreign molecules interact with cells of the immune system and where the B lymphocytes complete their maturation. The immune response can be classified into two broad categories: an *innate immune response* that can be non-specific and is executed by leukocytes (white blood cells) such as granulocytes, lymphocytes, monocytes, natural killer cells, mast cells and phagocytic cells (macrophages, dendritic cells, neutrophils) and a more specific or *acquired immune response* that mainly involves T lymphocytes and B lymphocytes. The so-called cellular immunity implicates the action of T lymphocytes, whereas humoral immunity involves B lymphocytes (Azpiroz et al. 2003).

The immune reaction following an infection can be local, in which case inflammation occurs caused by lymphocytes and other immune cells through the release of molecules called *cytokines*, such as interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF); or it can be systemic, a reaction characterised by the involvement of cytokines released by immune cells on distant tissues such as those of the nervous and endocrine systems (Aubert 1999).

There is very strong evidence for a nervous–immune–endocrine systems' multi-directional communication in health and disease (see for instance Vollmer-Conna 2001; Kaplin and Bartner 2005). In fact, such communication network is not an evolutionary novelty of the vertebrates but has deep evolutionary roots into simpler life forms such as the invertebrates (e.g. see the case of molluscs discussed in Vollmer-Conna 2001: 763). Indeed, cells of the immune system express receptors for neurotransmitters, hormones and neuropeptides. Hormones such as glucocorticoids (a group of corticosteroids) may facilitate or suppress immune function, whereas androgens, progesterone, adrenocorticotrophic hormone and, in general, also opioids tend to have a dampening effect on immunity. On the other hand, growth hormone, prolactin, thyroxine and insulin facilitate the immune response. Additional hormones that can be immunomodulatory are the catecholamines (adrenaline and noradrenaline), vasoactive intestinal peptide, P substance, somatostatin and Y neuropeptide (Azpiroz et al. 2003). In the same way as immunity can be affected by endocrine functions, the nervous system can also interact with components of the immune system. For instance, cells of the sympathetic peripheral nervous system innervate various lymphoid organs and the immune cells in those organs produce cytokines that in turn may interact with areas of the central nervous system, those controlling the expression of various emotions, behaviours and cognitive states during sickness in particular (Azpiroz et al. 2003). In general, almost all organs of the immune system are directly connected to the autonomic nervous system (McEwen et al. 1997b).

Immune System, Behaviour and Cancer Development

Given this broad interconnection between immune, endocrine and nervous functions, we may then ask: What are the fine mechanisms that link the activity of the immune system, the development of cancer and the expression of specific behaviours?

Many stressors, including cancer, activate the production of cytokines from the affected peripheral tissues. Cytokines are polypeptides that play a very important role in cell-to-cell communication across many tissues, including those of the immune system (see for instance Gupta 1988). Those cytokines (mainly IL-1 α , IL-1 β , IL-6 and TNF- α ; see Fig. 2.2 for a representation of the molecular structure of TNF- α) then trigger the production of endogenous brain cytokines that finally elicit sickness syndrome behaviours such as anorexia; sleeplessness; anhedonia; fatigue; pain; depression; altered learning, memory and other cognitive functions and decreased sexual behaviour (see Fig. 2.3) (Yirmiya et al. 1995; Johnson 1998, 2002; Larson and Dunn 2001; Pollak and Yirmiya 2002; Maier and Watkins 2003; Dantzer 2004, 2009; Lee et al. 2004b; Myers 2008; Ray et al. 2008). Peripheral cytokines communicate with the brain in various ways. They may diffuse through the blood–brain barrier, they may be actively transported or, by activating the vagus nerve, they may stimulate brain cells such as microglia to produce brain cytokines

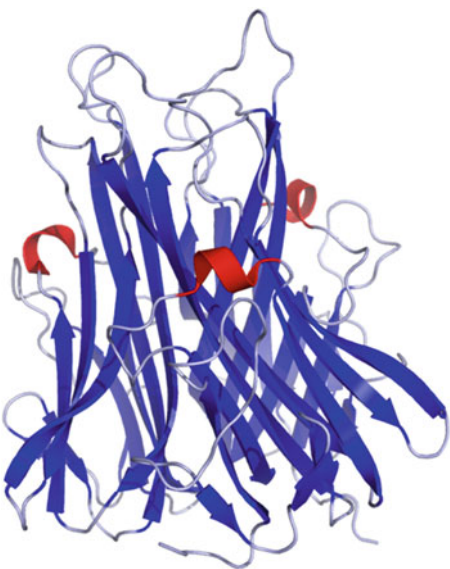


Fig. 2.2 Model of the molecular structure of tumour necrosis factor- α

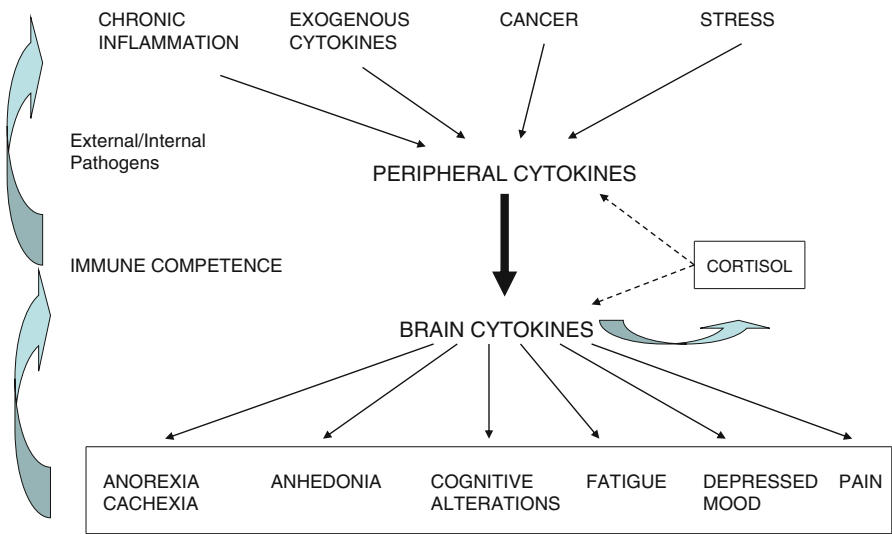


Fig. 2.3 Cytokine-mediated mechanisms for the effects of cancer and stress on behaviour. The various stressors are associated with increased production of peripheral cytokines. Cortisol is the main modulator of cytokines, and its production is enhanced by brain cytokines. Adapted from Dantzer (2004)

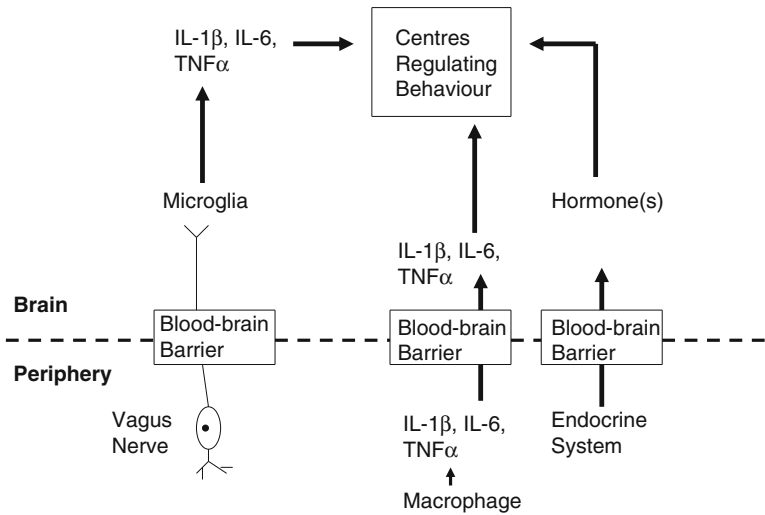


Fig. 2.4 Diverse mechanisms of action of cytokines on brain centres regulating behaviour. Cytokines produced by macrophages may directly cross the blood–brain barrier to affect brain activity, they may affect the brain indirectly via the action of hormones or they may modify the activity of the vagus nerve which will then stimulate brain internal production of cytokines by the microglia. From Johnson (2002) with modifications

Table 2.2 Comparison of the effects of cytokine administration with non-specific symptoms of sickness

Results of cytokine action on the central nervous system	Non-specific symptoms of sickness
General malaise	Feeling sick
Decreased activity	Loss of energy or fatigue
Decreased social investigation	Loss of interest in usual activities
Decreased food and water intake	Poor appetite
Weight loss	Significant weight loss
Sleep changes	Sleep changes
Fever	Fever

From Dantzer and Kelley (1989, see also Kelley et al. 2003)

(Johnson 2002, see Fig. 2.4). Cytokine production can be modulated by the corticosteroid cortisol (Dantzer 2004). The causal association between cytokines and sickness behaviours has also been shown experimentally through peripheral and direct brain administration of cytokines (Table 2.2).

It has been proposed that the expression of sickness behaviour in the context of cancer that is mediated by cytokines is in turn controlled by the transcription factor NF- κ B, which is involved in the regulation of both adaptive and innate immunity. It is also known that NF- κ B helps regulate responses to stress (Lee et al. 2004b). Production of NF- κ B is activated in tissues affected by different forms of cancer, from lymphoma to colorectal cancer and leukaemia (Lee et al. 2004b).

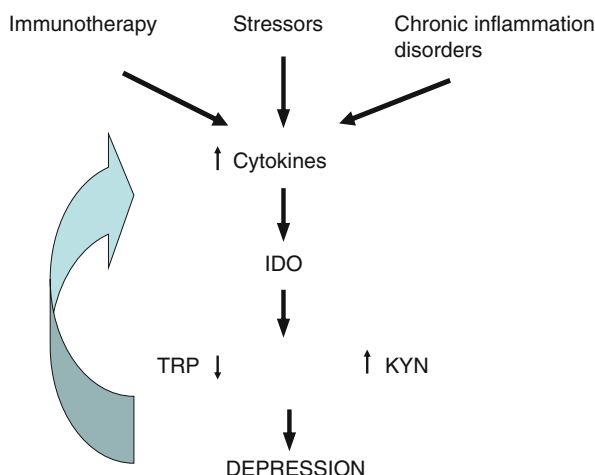


Fig. 2.5 Effects of cytokines on depression: Psychosocial stressors may activate the innate immune system, thus releasing cytokines into the blood stream. Such cytokines may then increase the activity of the enzyme indoleamine 2,3-dioxygenase (IDO) which degrades tryptophan (TRP), thus producing kynurenine (KYN). More kynurenine leads to a depressed mood. Subsequent changes in immune states may follow the initial depression that can further increase cytokine activity (adapted from Dantzer 2009)

Cytokines, Depression and Cancer

The *stress response* is an organism's reaction to external (or even internal, see Lazarus et al. 1985) stimuli producing an adaptive response of the organism that involves "intense nervous arousal with consequent stimulation of the hypothalamic-hypophyseal-adrenocortical axis and generalised adrenergic responses" (Selye 1976: 54). The stress response affecting activities of the immune system leads to the expression of the *sickness syndrome*.

Although the stress response may be adaptive as an expression of generalised arousal in the face of danger (Selye 1975), it may also take forms that could be more pathological as in the case of *distress* (Selye 1976), potentially leading to depression when it is sustained over time. From a molecular perspective, the link between stress and depression with cancer is arguably one of the most promising areas of research in behavioural oncology. The specific molecular mechanisms linking stress and depression via the action of cytokines are summarised in Fig. 2.5. Cytokines released under stress activate the production of indoleamine 2,3-dioxygenase (IDO), an enzyme that metabolises tryptophan into kynurenine and quinolinic acid. Increased kynurenine metabolites trigger the symptoms of depression (Raison et al. 2010). As depression increases, the effect of stressors on this whole process becomes reinforced, thus producing a vicious circle leading to more sustained levels of depression.

According to Robert Dantzer (see Dantzer and Kelley 2007; Dantzer et al. 2008), it was Ronald S. Smith first and then Michael Maes who initially associated the

activation of the immune system with depression in humans. What Smith and Maes had in mind was a central role for pro-inflammatory cytokines, such as IL-1, in releasing a depressive psychological mood (Smith 1991; Maes 1993; Maes et al. 1995; Raison and Miller 2003). For instance, cancer patients who undergo treatment with cytokines such as IL-2 and interferon- α (IFN- α) can be specifically affected by depression (Capuron et al. 2000, see also Kelley et al. 2003).

In rodent models, IL-1 β depresses social exploration (Goujon et al. 1995) and also has dampening effects on memory consolidation, various forms of fear conditioning and long-term potentiation (this is a facilitation of specific molecular processes and finally behaviours) through its actions on both the hippocampus and the amygdala (Kelley et al. 2003). Pro-inflammatory cytokines also render central nervous system regions, such as the hypothalamus–pituitary axis, hyperactive through the local release of neuropeptides such as corticotropin-releasing hormone and vasopressin which may be associated with depression (Dantzer et al. 2008); cytokines also depress sexual behaviour in female rats (Avitsur and Yirmiya 1999).

Metastatic colorectal cancer patients, especially those displaying abnormal 24-h rest/activity patterns, have higher circulating levels of the cytokine transforming factor- α , TNF- α and IL-6. The same patients also show levels of emotional and social functioning that are categorised as poor and display both fatigue and loss of appetite (Rich et al. 2005, see Vissoci Reiche et al. 2004 for a review).

Cytokines also mediate the following behavioural changes in cancer patients that are observed in depressed individuals: cognitive dysfunction such as distraction, loss of memory and multitasking difficulties; and they also mediate loss of executive functions and motor abilities (see Myers 2008 for a recent review). With regard to cognition, cytokines such as IFN- α can have specific effects on information processing, frontal lobe functions and verbal memory. IL-2 and TNF- α are also capable of producing cognitive and psycho-motor alterations in cancer patients such as broader memory deficits, difficulties with motivation and flexibility of thinking, decreased attention, lack of coordination of motor faculties and depression. Many of those cognitive effects are mediated by cytokines through their action on the hippocampus in particular (see Lee et al. 2004b for a review). These effects of cancer on behaviour that are mediated by cytokines mirror similar effects produced by external antigens. For instance, in an experimental study of 20 male volunteers who were injected a safe amount of *Salmonella abortus equi* endotoxin (0.8 ng/kg), the injection was followed by an increase in circulating levels of TNF- α , IL-6 and cortisol. Volunteers also showed an associated increase in their degree of anxiety and depressed mood and a decrease in both verbal and nonverbal memory (Reichenberg et al. 2001, see also references therein about other similar experiments).

In the case of cancer patients undergoing immunotherapy as part of their treatment, the therapy itself can cause the sickness behaviours: some changes in cognitive abilities and increased irritability and anxiety leading to depression (Dantzer et al. 2008).

In rodents, the following brain regions express the cytokine IL-1: hippocampus, cortex, amygdala, hypothalamus, thalamus, dentate gyrus and cerebellum (Dantzer 2009) and IL-1 receptors are found in cells of the dentate gyrus, anterior pituitary

gland, pyramidal cell layer of the hippocampus and in association with the preoptic and supraoptic areas of the hypothalamus and the cortex among others (Dantzer et al. 2008). Cytokines are also expressed in the nucleus tractus solitarius, bed nucleus of the stria terminalis and circumventricular organs (Pecchi et al. 2009). Therefore, the many behaviours controlled by those brain regions (sexual, social, memory, problem solving and so forth) may be also affected by cytokines as they are released during a state of illness.

In sum, stress and immune activity during illness result in the behaviours that characterise the *sickness syndrome* and eventually depression, with cytokines being key molecular mediators in such a process.

Activation of the immune system during cancer development may also produce a response of such magnitude that immunity overshoots, so to speak, starting an attack against healthy tissues. This may lead to what are known as *autoimmune paraneoplastic disorders* (APDs), that is, disorders produced by a hyperactivated immune system that attacks healthy tissues in response to cancer development. When the healthy tissue is part of the nervous system, effects on behaviour can also be expected. Such an autoimmune attack is believed to be possible when cancer cells express molecules that are also expressed by neurons (*onconeural antigens*) (Dropcho 1995; Darnell 1996, see also Eichmuller and Bazhin 2007 for a recent review). Various areas of the brain can be affected by APDs, including the limbic system, cerebellum, brainstem, retina, dorsal root ganglia and spinal cord (Darnell 1996; Abu-Shakra et al. 2001, see Darnell and Posner 2003 for a review). Towards the end of this chapter we see the specific case of autoimmune paraneoplastic retinopathy affecting visual capabilities.

Hormones, Stress and the Link with Cancer

Hormones are molecules that are produced in specific tissues and exert a regulatory action on the activity of cells of the same tissue (autocrine hormones), adjacent tissues (paracrine hormones), other tissues within the same individual (endocrine hormones) or tissues in other individuals (exocrine hormones).

A particular hormonal link between the development of cancer and behaviour is represented by oestrogens. Oestrogens are steroid hormones present in both males and females that are mainly (but not exclusively) produced by the gonads. Leena Hilaviki-Clarke (1997) proposed that oestrogens can be mediators between behaviour and development of breast cancer. For instance, circulating oestrogens affect the expression of depressive mental states, with depression being associated with low oestrogen levels. At the same time as levels of oestrogens decrease, risks of developing breast cancer become lower. High plasma oestrogens, with their associated higher risk of breast cancer development, are also characteristic of women with difficulties expressing hostile emotions. However, this positive association between circulating oestrogens and breast cancer development is valid for older women. In the case of premenopausal women the relationship seems to be reversed:

likelihood of developing breast cancer may be associated with low-circulating oestrogens and hence greater levels of depression. In fact, Bodhankar et al. (2012) have suggested a protective effect of oestrogens against immune-mediated inflammatory diseases. Perhaps oestrogens are less protective against cancer at older ages due to a broad trend towards immune dysregulation with increasing age? Oestrogens have also various cognitive effects such as memory improvement, suggesting that memory impairment during cancer could be explained, at least in part, by low oestrogen levels. On the other hand, in rodent models, high circulating levels of oestrogens in males, leading to cancer development in the liver and prostate for instance, are associated with elevated aggressiveness (Hilaviki-Clarke 1997). Mulder et al. (1992), however, are more sceptical about the association between the expression of oestrogen receptors in cells of the mammary tissues and both progression of breast cancer and sickness behaviours.

Prostaglandins also play an important role in the expression of sickness behaviour. This is particularly so for prostaglandin E2 whose production is triggered in the brain by cytokines (Pecchi et al. 2009). At the same time, prostaglandin E2 has been linked to cancer progression (e.g. Timoshenko et al. 2003), and both prostaglandins and catecholamines can affect cancer recurrence (Neeman et al. 2012), being also involved in the stress response (e.g. Munhoz et al. 2008). It is still uncertain, although plausible, whether chronically high levels of insulin-like growth factor-1 (IGF-1) that are associated with breast cancer development are also a result of chronic depression (Moyad and Pienta 2002).

The sickness syndrome mediated by cytokines can also involve the release of glucocorticoid hormones into circulation. Glucocorticoids, in turn, can downregulate the action of various cytokines in the brain. Apart from glucocorticoids, there are other molecules that can also affect cytokine activity: the prostaglandins and oestrogens that we have already mentioned, IL-10 (an anti-inflammatory cytokine) and various peptides such as α -melanocortin, insulin-like growth factor 1 and vasopressin (Ruh et al. 1998; Konsman et al. 2002).

Glucocorticoids are well-known modulators of the immune response to stress. Historically, our understanding of the relationship between immunity and glucocorticoids has been characterised by an emphasis on what are two misleadingly alternative views. On the one hand, Hans Selye suggested that glucocorticoids may enhance at least some aspects of the immune response, and on the other Alan Munck highlighted the role of glucocorticoids in dampening the immune response and therefore preventing it from overshooting. That glucocorticoids may in fact exert both kinds of permissive and depressive actions on the immune system was subsequently emphasised by Bruce McEwen and collaborators in a review article published in *Brain Research Reviews* (McEwen et al. 1997b, see also references for Selye's and Munck's works there). Table 2.3 lists a sample of both permissive and depressive effects of glucocorticoids on cells of the immune system. In addition, glucocorticoids may not just increase or decrease the production of immune cells, but they may also affect the redistribution of available cells (e.g. lymphocytes) across tissues to facilitate their reaching those parts of the body where they may be most needed (Munck et al. 1984; Munck and Guyre 1991). In other words, the role of

Table 2.3 Effects of glucocorticoids on immune cells

	By these cells
Increase	
Insulin receptors	Human lymphocytes
β-Adrenergic receptors	Human lymphocytes
High-affinity VIP receptors	Human monocytes
Ig E stimulation by IL-4	Human lymphocytes
IgG, IgA, IgM	Human lymphocytes
IgA levels in serum	Intact rats
Decrease	
IL-1, 2, 6, 8, 12 production	Various types
TNF, granulocyte colony stimulation factor	Various types
MHC-1 or MHC-2 or both	
Fc receptor on granulocytes	Human granulocytes
Eicosanoid biosynthesis	Macrophages
Proenkephalin mRNA	Rat B cells

VIP vasoactive intestinal peptide, *MHC* major histocompatibility complex
From McEwen et al. (1997b)

glucocorticoids and perhaps other molecules affecting the immune system is more one of regulating the activities of such system than anything else. When the immune system becomes dysregulated, as a result of chronic stress for instance, disease is more likely to develop (see Godbout and Glaser 2006 for a review).

The mechanisms of the stress response that is mediated by corticosteroids are worth further consideration as stress is an important candidate link for an association among behaviour, neuro-immuno-endocrine system and cancer (see Fig. 2.6).

So far, we have emphasised molecular and physiological mechanisms that from stress (derived from cancer development, for instance) lead to sickness behaviours, potentially resulting in depression. Such link is mediated by cytokines, other components of the immune system, hormones and their effects on both the central and peripheral nervous system. But the converse relationship is of equal if not greater interest: Can sustained levels of stress, psychological stress in particular, conduce to cancer development? What are the molecular and physiological mechanisms that could mediate such a causal link?

The kind of stress that is of most interest in this book is *psychological stress* that could be defined as “a negative emotional experience accompanied by predictable biochemical, physiological, cognitive and behavioral changes that are directed either towards altering the stressful event or accommodating to its effects” (Dimitroglou et al. 2003: 39, following Baum 1990). In principle, psychological stress could potentially affect the onset of cancer (*initiation*) and/or its *promotion* or further progression, including progression into a *metastasis* stage (Justice 1985, see Antoni et al. 2006 and also Lutgendorf and Sood 2011 for recent reviews). However, *acute* (short duration) psychological stressors are more likely to elicit an adaptive response, whereas *chronic* psychological stressors (sustained over time) could lead to decreased health. Acute psychological stress tends to be associated with an adaptive activation of immunity, whereas chronic stress can result in immune suppression

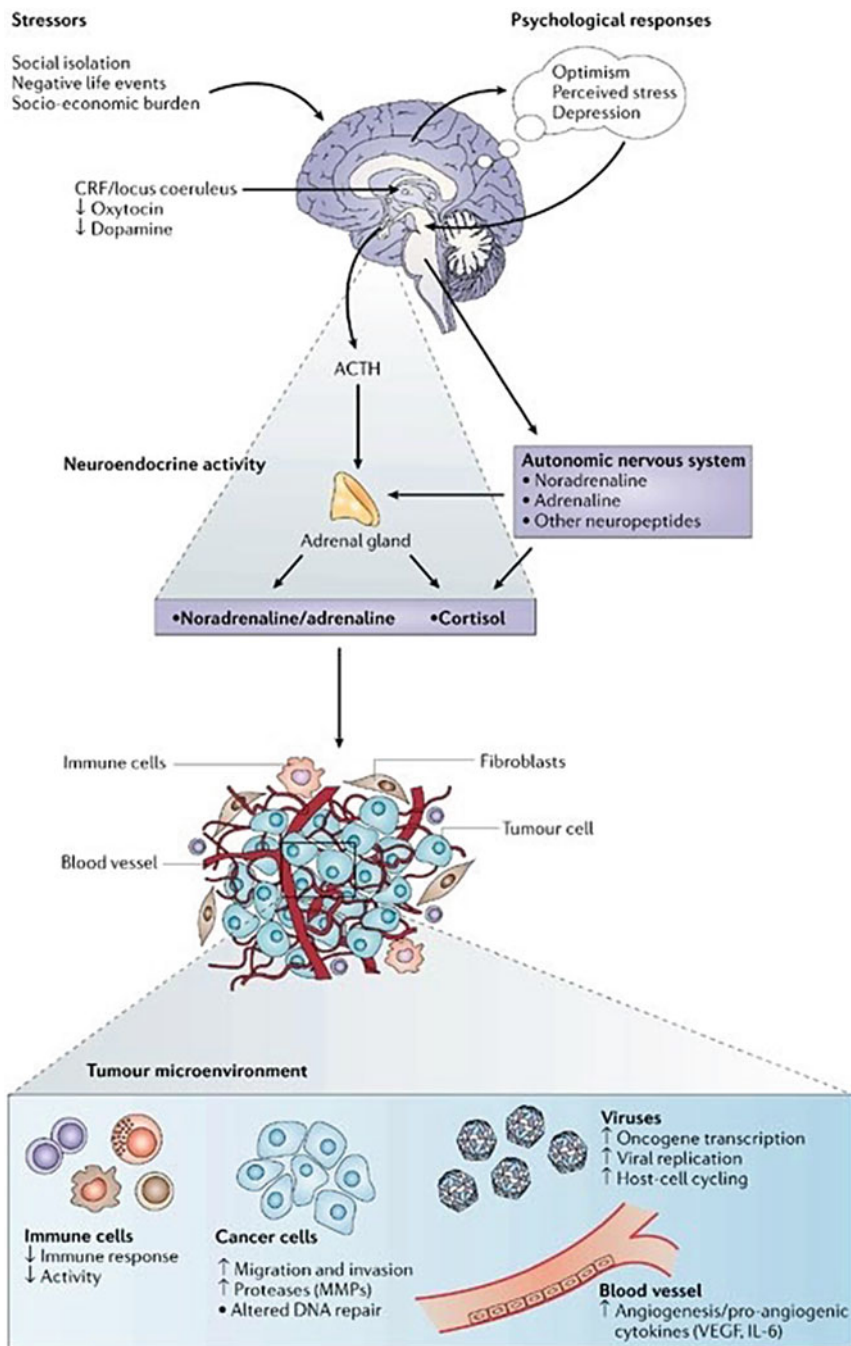


Fig. 2.6 Mechanisms linking psychological stress with neuro, endocrine and immune activity that can then modulate the onset and progression of cancer. The central nervous system responds to various kinds of external behavioural stressors by producing mental states that could increase or decrease the perception of stress and the production of various hormones through the activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Release of hormones such as cortisol and catecholamines may affect tumour development and metastasis; this latter capacity is also favoured by pro-angiogenic cytokines that favour the growth of blood vessels around the tumour that could subsequently provide the conduit for its spread to other parts of the body (from Antoni et al. 2006)

(Dhabhar 2000) or, more generally, immune dysregulation (Godbout and Glaser 2006) with potential consequences for decreased defences against cancer.

Let us start with the first issue: the potential role of psychological stress in the initial development of cancer from a healthy state. Can psychological stress leading to intense and sustained states of distress cause cancer? More specifically, given that a cell becomes cancerous following specific kinds of mutations or epigenetic changes, the question should be better rephrased so: Can sustained psychological stress cause specific mutations or epigenetic changes that may transform a normal cell into a cancerous one?

The short answer is yes, it potentially can (see Gidron et al. 2006 for a review; see also Gidron and Ronson 2008; Lutgendorf and Sood 2011). Counter to some initial sceptical reviews (such as Fox 1995) that were less than impressed with the available evidence linking psychological stress with onset and development of cancer, more recent work has thrown more light on such a link. In what follows we should keep in mind that cancer starts as a molecular change in a single cell. Therefore if sustained levels of distress have any chance of promoting cancer development they must necessarily be associated with increased molecular changes, such as mutation rate or alterations in the patterns of DNA methylation, in specific tissues (Feinberg and Henikoff 2005). For instance, Fischman et al. (1996) stressed albino Sprague Dawley rats by constraining them to swim in either cold water (2 °C) or warm water (28 °C) and compared the number of chromosome aberrations experienced by those experimental rats with controls that were not stressed in any obvious manner. Both stresses were associated with an increase in chromosome aberrations, which are sources of genetic changes. In a second experiment, Fischman and collaborators subjected five groups of four rats each to “no stress”, “swim stress”, “noise”, “intermittent foot-shock” and “continuous footshock”. Again, in all cases stressors increased the number of chromosome aberrations. Stress is associated with the suppression of the synthesis of methyltransferase in rats, a DNA repair enzyme (Glaser et al. 1985), an effect that should predispose DNA to experience increased rates of mutation.

Parker et al. (2004) subjected 40 female hairless mice (strain SKH:H-1-hrBr) to a “naturalistic stressor”, the odour of fox urine, for 14 days. There were also 40 control mice. All mice were subsequently irradiated with UV light (that causes mutations) three times a week whilst continuing to be exposed to the stressor also three times a week. On a weekly basis they were checked for skin lesions and tumours. Tumours appeared earlier in stressed mice than in controls, and after 21 weeks the difference in number of tumours (mainly squamous cell carcinomas and some papillomas) between experimentals and controls was fivefold, with 35 % of stressed mice developing at least one tumour, as compared with only 7 % of controls.

Flint et al. (2007) subjected 3T3 fibroblast cells cultures to cortisol, norepinephrine or epinephrine treatment, three hormones released under stress, and studied the ability of those cells to repair their damaged DNA following exposure to ultraviolet light. Hormone-treated cells suffered significantly more DNA damage than control. That the damage was mediated by the hormones was further confirmed by incubating cells with the glucocorticoid receptor antagonist RU486 and the catecholamine receptor antagonist propranolol which prevent the action of cortisol and epinephrine and norepinephrine, respectively. 3T3 fibroblasts so incubated did not differ from

controls in the degree of damage to their DNA. The authors also measured the effect of those stress hormones on expression of a series of genes and found that the hormones modulate the expression of genes directly involved in the processes of DNA repair and damage.

Immobilisation stress has also been shown to induce prostate cancer progression in mice (Hassan et al. 2013).

In humans, Dimitroglou et al. (2003) studied 15 men and 15 women considered to be “psychogenically stressed” due to them having been in the care of a child with cystic fibrosis, a chronic disease, for not less than 7 years. They were compared with 15 control men and 15 control women in their level of stress (measured through the *State-Trait Anxiety Inventory*). Individuals attending a cystic fibrosis child were more stressed than controls. This differential level of stress was associated with increased DNA damage in lymphocytes in stressed individuals as compared with controls, after exposure to either hydrogen peroxide (H_2O_2) or γ -radiation.

Stress in psychiatric patients has been associated with deficient DNA repair in their X-ray-irradiated lymphocytes (Kiecolt-Glaser et al. 1985), whereas stress in medical students is associated with inhibition of apoptosis in leukocytes that have been exposed to γ -radiation (Tomei et al. 1990).

Therefore specific mechanisms have been identified that can link stress with mutations and subsequently cancer development. But once a tumour has developed, it is well known that stress can also enhance its progression. In rodent models for instance, behavioural stressors such as confrontation, restraint, forced swim and social isolation may increase growth of tumours and probability of metastasis (see review in Antoni et al. 2006).

Steven Cole and Anil Sood (2012) have recently reviewed some key aspects of the physiological links between stress and cancer progression that are crucially affected by the activation of the sympathetic nervous system. Haematopoietic malignancies (such as lymphoma and leukaemia) and metastasis of solid epithelial tumours are especially sensitive to the effects of a stress-activated sympathetic nervous system, leading to cancer progression.

Psychological Stress, Reactive Oxygen Species and Cancer Development

One important molecular mechanism linking stress and onset and further development of cancer implicates reactive oxygen species (ROS). Normal immune responses against an infectious agent involve the production of ROS that if maintained at high levels for a prolonged period of time in a condition of chronic inflammation may promote the development of cancer (Greaves 2000; Reuter et al. 2010). Moreover, chronic inflammation can result also from non-infectious causes (Karin and Greten 2005) such as chronic psychological stress (e.g. Lu et al. 2013). ROS are molecules containing oxygen that are a product of aerobic metabolism. They include hydroxyl radicals ($\cdot\text{OH}$), superoxide anions ($\text{O}_2^{\cdot-}$), singlet oxygen ($^1\text{O}_2$) and hydrogen peroxide (H_2O_2) (see for instance Matés and Sánchez-Jiménez 2000). ROS are highly

reactive and may cause oxidative damage to cells, including mutations to their DNA that may be carcinogenic, unless ROS are neutralised by antioxidants (such as vitamins C, E, β -carotene). One mechanism of defence against DNA damage caused by ROS, or any other mutagen, is programmed cell death (apoptosis), but if mutations affect the ability of the cell to undergo apoptosis, then the mutated cell may reproduce unchecked leading to cancer.

Psychological stress may also lead to oxidative damage of cellular DNA. Adachi et al. (1993) used 6-week-old male Sprague Dawley rats as an experimental model to study whether psychological stress, in the form of conditioned emotional stimuli, would be associated with DNA damage. DNA damage due to oxidative stress was estimated through measuring the level of 8-hydroxydeoxyguanosine (8-OH-dG) in nuclear DNA, 8-OH-dG being produced in cells by endogenous ROS. Some of the rats (senders) were stressed by direct application of an electric shock, whereas others (responders) were visually, auditorily and olfactorily exposed to the electric-shocked animals. Responders increased their levels of 8-OH-dG after several (two, three, four) exposures to senders and decreased those levels after exposure terminated. That is, psychological stress, when sustained, can produce actual alterations to DNA in rats, potentially leading to the onset of cancer.

ROS resulting from psychological stress can also affect the probability of onset and progression of cancer in humans (Irie et al. 2005 and references therein). Irie et al. (2005, see also their previous works cited therein) have shown that psychological stress, especially when it leads to depression, is followed by increased 8-OH-dG levels in circulating leukocytes in healthy individuals. In particular, higher 8-OH-dG levels were detected in females in association with depression and inefficient stress coping strategies, whereas in males 8-OH-dG levels were positively associated with stressful life events and long working hours. In a study carried out on 30 outpatients (20 males and 10 females) diagnosed with depression and 60 healthy controls, Irie et al. (2005) found an association in the responses of participants to a questionnaire (*Center for Epidemiological Studies Depression scale* and *Profile of Mood States* items) with their levels of 8-OH-dG in circulating leukocytes. Outpatients were significantly more depressed than controls, and they also had more elevated circulating relative levels of 8-OH-dG ($0.53/10^5 \text{ dG} \pm 0.52$) than controls ($0.29/10^5 \pm 0.12$).

Gidron et al. (2006) have recently reviewed the relationship between sustained psychological stress and damage to DNA by ROS in both rodents and humans. With regard to humans, they list 13 published works indicating that distress, depression and anxiety are more often than not associated with poor DNA repair capabilities, decreased levels of apoptosis, more DNA damage and lower antioxidant levels. Moreover, available evidence also suggests that some coping strategies in the face of stress are ineffective in preventing stress-related DNA damage. For instance, engaging in wishful thinking and daydreaming about the resolution of problems rather than taking effective action is a recipe for increased stress-related DNA damage. Interestingly, some studies have associated the stresses suffered by children at a young age, boys in particular, resulting from a distant relationship with parents, with an increase in DNA damage. Although this claim must still be backed up by

better designed studies, it is an issue certainly worth investigating (see for instance Taylor 2010 for a discussion of the mechanisms associating stresses during early life and adult health problems). With regard to sex-specific associations between psychological stress and damage to DNA, Gidron et al. (2006: 301) conclude that:

In women, negative moods, tension and ineffective stress-coping strategies, psychological stress at work and little prospect of stress alleviation were all related to greater DNA-damage. Men's DNA-integrity may have been adversely affected when they had suffered bereavement in the last year, adopted self-blame strategies, and perceived high workloads.

Men can be especially susceptible to suffer DNA damage and therefore develop cancer when they already manifest distress-related psychological disorders such as generalised anxiety disorder (GAD). In a recent study carried out in Taiwan, Shen et al. (2013) followed up adult individuals who had been diagnosed with GAD—and had no other known malignancies—from 2000 to 2010. They studied 19,793 patients (35.6 % of them being men). Over the period of follow-up 559 cases of cancer were recorded, giving a value of the standardised incidence ratio (SIR) of 1.14, which indicates that this population of GAD patients was at higher risk of developing cancer than the general population. Higher risk of cancer development was observed especially for the case of lung, mediastinum and prostate cancer, which were more likely to develop in male GAD patients.

Psychological Stress, Telomere Length and Cancer

One aspect of DNA damage that is associated with psychological stress involves the length of telomeres. Telomeres are complexes of DNA and proteins that are found at the ends of chromosomes and that protect the chromosome from damage. Telomeres, however, shorten after each DNA replication, but they are repaired and protected by the action of the enzyme telomerase. Molecular processes that affect telomere length, such as mutations in the telomerase gene and oxidative stress, may lead to DNA damage (see Epel et al. 2004; Simon et al. 2006a) and hence, potentially, to cancer.

The effect of psychological stress on telomere length has been shown by various authors. Simon et al. (2006a) studied 88 individuals diagnosed with either major depressive disorder or bipolar disorder and compared them with controls. Control individuals had telomeres that were longer (7.64 kb on average) than those of individuals presenting a mood disorder (6.89 kb on average, both disorders combined), after controlling for confounding variables. Epel et al. (2004) studied 58 premenopausal women who had either a healthy child or a chronically ill child. Presumably, women attending a chronically ill child were under greater stress than women attending a healthy child. Epel et al. measured both “perceived stress” which was assessed through a questionnaire and “objective” stress estimated through the number of years mothers had been taking care of their child. Telomere length decreased with increased perceived and actual stress; telomerase activity also decreased in both cases, whereas the levels of oxidative stress increased. O'Donovan et al. (2009) recruited 36 post-menopausal women (51–79 years old); 23 of them were caring for

a relative suffering from dementia, a situation that is expected to subject such caregivers to a significant level of stress, and 13 (controls) were not caregivers. They found that caregivers had shorter telomeres than non-caregivers.

Alterations of telomere length have been associated with cancer development (see Blasco 2005 for a review).

Apoptosis and Cancer Development

As already mentioned, a cancer-causing mutation could be quickly eliminated if the mutant cell undergoes apoptosis (programmed cell death). If apoptosis fails to eventuate, then cancer may progress. Can behaviour enhance the ability of cells to undergo apoptosis and therefore protect the organism against cancer cell proliferation? And conversely, can behaviour prevent apoptosis and in so doing facilitate the spread of cancer cells?

Sendo et al. (1997) have studied the effect of psychological stress and glucocorticoids on apoptosis of neutrophils, one of the various types of white blood cells that are heavily involved in defence against cancer in humans. However, given the ability of neutrophils to produce ROS, they may be also cause of cancer development unless their individual lifespan is relatively short, which it normally is (about 5–6 h). But if lifespan is extended due to interference with the mechanisms of apoptosis then they themselves could potentially give rise to a cancerous lineage, a sort of coup d'état by the army that is there to protect us against foreign invasion. Sendo et al. (p. 513) recount an incident that suggested to them that stress could mediate such a change in neutrophil lifespan:

During a series of experiments on neutrophil apoptosis, one of the authors was asked to donate a sample of blood for neutrophil apoptosis examination. After finishing the experiment, the experimenter [noticed] that the neutrophils had not undergone apoptosis. A discussion on the reason for this outcome led to the possibility that it resulted from the author not sleeping well the previous night.

They then decided to carry out a proper test of the hypothesis by using a group of volunteers who had a smaller than normal time for sleep; again the volunteers had apoptosis-resistant neutrophils compared with a group of controls who had normal amount of sleep. This kind of stress therefore may favour the conditions for cancer development in neutrophils, but what about chronic or longer term psychological stress? Sendo et al., using a human model of students under academic examination, showed that longer term stress is in fact associated with increased levels of apoptosis in neutrophils. Although increased apoptosis may defend the organism against the possibility of neutrophils becoming cancerous, given that these are cells of the immune system that may help destroy cancerous cells in other tissues and also carcinogenic pathogens, increased neutrophil apoptosis may in turn enhance the probability of cancer in those tissues. Perhaps in this case the initial increase in neutrophil lifespan due to a short-term stress may indeed be a functional response, as the body may “read” the state of stress as an “indication of infection” for instance; hence, the longer lifespan of neutrophils could be adaptive, whereas longer term stress is more

likely to produce the conditions favouring cancer through, in this case, increased neutrophil apoptosis. Still, the possibility remains plausible that if decreased immune cell apoptosis is sustained over time, this may lead to longer cell lifespan and potentially cancer whenever immune cells may suffer somatic mutations for instance, as it may happen to lymphocytes (e.g. Burkhardt-Schultz et al. 1996). See also the case of B lymphocyte-dependent cancers (de Visser et al. 2006) and neutrophilic leukaemia (Böhm and Schaefer 2002).

Using a BALB/c mice model, Shi et al. (2003, see also Yin et al. 2000) showed that mice stressed through physical restraint had about 35–40 % decrease in the number of splenic lymphocytes compared to controls. This reduction was due, at least in part, to apoptosis. In this case stress seems to favour cell apoptosis, but again, because the effect involves cells of the immune system, greater apoptosis may result in immunodeficiency, thus leading to greater susceptibility to developing cancer in other tissues. Such apoptotic effect of stress on lymphocytes was regulated by endogenous opioids.

Clearly, the take-home message from these studies is that you just do not mess up with the apoptosis of your immune cells: too much and you become immunocompromised (thus increasing cancer risk in other tissues), as it could happen in conditions of chronic stress. Too little and you give immune cells free rein to run amok, thus potentially becoming cancerous themselves (de Visser et al. 2006). Another cellular process that can have a dual promoter or suppressor role in cancer is *autophagy*, a mechanism by which cells degrade first and then recycle large molecules and organelles, especially when deprived of nutrients (Kondo et al. 2005; Maiuri et al. 2007). Cell autophagy may increase in conditions of long-term physiological stress (Crotzer and Blum 2005) but it remains unclear whether the same may occur for the case of psychological stress.

Epigenetic Mechanisms: Psychological Stress, DNA Methylation and Cancer

We have already mentioned that cancer can develop following either specific genetic mutations or epigenetic alterations in cellular DNA. Epigenetic changes such as methylation, hypomethylation and hypermethylation can affect gene expression without altering the nucleotide sequence of the gene. Both hypomethylation and hypermethylation can be associated with increased cancer risk, as in a condition of low methylation oncogenes may fail to be silenced (suppressed), whereas hypermethylation may silence genes involved in the defence against cancer. Methylation in turn is responsive to the degree of psychological stress that the individual is subject to throughout his/her life (Alegria-Torres et al. 2011). Corticosteroids released under stress in particular can mediate such interference of stress with epigenetic mechanisms and hence cancer development (Antonova and Mueller 2008).

Some recent studies have carried out specific investigations of the relationship between psychological stress and epigenetic mechanisms that illuminate their relevance in the onset of cancer. Rusiecki et al. (2012) focused on post-traumatic stress

disorder (PTSD) suffered by American soldiers returning from the wars in Iraq and Afghanistan. PTSD has been linked to epigenetic processes affecting both the silencing and activation of the transcription of genes via the modulation of methylation. Moreover, such altered methylation in PTSD patients can specifically affect genes involved in immune functions. A total of 75 cases of PTSD and 75 controls (randomly sampled army and marine service members) were analysed by Rusiecki and collaborators. The total sample comprised 33.3 % females, 80 % Caucasians. Soldiers were found to display evidence of both hypo- and hypermethylation both after deployment in a war zone and in association with the development of PTSD.

In a recent study of 109 children (61 % girls) and their parents who were part of the *Wisconsin Study of Families and Work* (WSFW), Essex et al. (2013) measured parental stress at various times from infancy to preschool ages of their child. DNA methylation in children was affected by both maternal and paternal stresses.

Unternaehrer et al. (2012) studied DNA methylation of two genes potentially associated with stress: the oxytocin receptor gene (*OXTR1* and *OXTR2*), which mediates the effect of oxytocin on the hypothalamo-pituitary-adrenal axis, and the brain-derived neurotrophic factor (*BDNF*) gene which has been found to be less active in individuals diagnosed with stress-associated mental disorders (e.g. PTSD). The authors studied the changes in DNA methylation in such genes in response to an acute psychological stressor in 76 adults (56.5 % women; about 64 years old on average) in Germany. Participants were born during or soon after WWII (1942–1947). The experimental psychological stressor consisted in a mock job interview and arithmetic exercises performed in front of a male and a female expert. Levels of DNA methylation increased in *OXTR1* from pre-stress to post-stress, but such methylation subsequently decreased with time. *BDNF*, on the other hand, was unaltered after the application of the acute psychological stress, but the gene is known to be affected by chronic stress. The effect of chronic stress on *OXTR* methylation is unknown (Unternaehrer et al. 2012: 1). Both *OXTR* and *BDNF* have been implicated in the progression of some cancers (e.g. prostate cancer) (Rennebeck et al. 2005; Zhong et al. 2010).

Thus, stress-related changes in DNA methylation could add to the other mechanisms that we have reviewed above and that link stress with cancer (see also Nasset 2012 and references therein).

Additional Mechanisms Linking Stress and Cancer Development

Chronic inflammation has also been associated with cancer development that could be mediated by cytokines, ROS, metabolites of arachidonic acid (e.g. prostaglandins) and chemokines (i.e. small cytokines that control chemically guided cell movement or chemotaxis). A long-term exposure of tissues to such mediators may result in higher levels of mutagenesis, activation of oncogenes, cell reproduction (decreased apoptosis) and also angiogenesis (i.e. development of new blood vessels) that will facilitate not only the production of cancer cells but also their metastasis or

movement to other areas of the body. Chronic inflammations have been associated with development of various tumours, especially carcinomas (i.e. tumours of epithelial origin): colon carcinoma, oesophageal adenocarcinoma and cancer of the stomach, but liver cancer and lymphoma may also be affected (see Shacter and Weitzman 2002 for a review). Chronic inflammation may be caused by chemicals of environmental origin such as industrial pollutants, or by viruses, bacteria and parasites, but it can also be caused by factors that are internal to the organism, such as chronic oesophageal reflux and ulcerative colitis. Psychological stress can also be a cause of chronic inflammation (e.g. Black 2002). Thus behaviour could affect cancer onset and/or progression whenever it can cause or enhance chronic inflammation. Psychological stresses affect the release of cortisol and catecholamines (e.g. as in the case of chronic depression) that in turn can alter the immune function, thus leading to chronic inflammation (e.g. Cohen et al. 2007).

Hence, depression resulting from stressful experiences, that in the short term may be an adaptive response within the sickness syndrome, may become a mental pathology and also a cause of diseases such as cancer, if it is intense, protracted over the long term, and no effective coping mechanisms are enacted to counteract it.

It should be noted that although there is a current emphasis on the activational response of the nervous, immune and endocrine system to a situation of illness and therefore stress (see for instance de Beaupre et al. 2005, but also Dunn et al. 2005 for counter-examples), behavioural depression caused in initially healthy individuals by stressful social interactions can also be associated with a decrease in the activity of the immune system (Weisse 1992, see Dhabhar 2009 for a review of both immune-protective and immune-inhibitory effects of stress) and hence higher susceptibility to developing a disease if sustained over time. That is, the causation can go from developing cancer first to then expressing a depressive state of mind as a result of stress-induced immune system activation or from being behaviourally depressed first to subsequently developing cancer as a result of corticosteroid/catecholamine-induced immunosuppression (Dunn et al. 2005; see also Fig. 2.6). Behavioural and cognitive changes following such stress are a result of the activity of specific areas of the brain such as the hippocampus, periaqueductal grey, amygdala, hypothalamus and other centres (McEwen et al. 1997a).

Evidence for the immunosuppressive effects of sustained stress in humans is abundant. In a meta-analysis of the literature available at the time, Herbert and Cohen (1993) showed that stress caused by psychological factors in humans is negatively associated with immune competence. For instance, stress tends to decrease the lymphocyte and NK cell capacity to respond to an antigen. In addition, there is also a negative association between stress and immunoglobulins (salivary IgA and serum IgM). In a study carried out by Tjemslund et al. (1997), post-surgical breast cancer patients showed a negative correlation between two measurements of anxiety and circulating numbers of B and T lymphocytes, whereas depression was negatively correlated with B and T4 lymphocytes. Such stress-induced immunosuppression may lead to cancer development (e.g. Saul et al. 2005). Table 2.4 lists some of the inhibitory and also enhancing effects that various stressors may have on the activity of the immune system in humans.

Table 2.4 Changes in the immune system of humans associated with stress

Representative effects	Stressor
Increased number of neutrophils	Spaceflight
Decreased lymphoproliferation following mitogen stimulation	Bereavement
Reduced lymphocyte cytotoxicity	Life change
Increased interferon production	Noise, sleep deprivation
Decreased interferon production	Medical school final examination
Decreased phagocytosis	Life change
Decreased natural killer cell activity	Medical school final examination
Decreased helper and suppressor T cell percentages and helper-to-suppressor ratio	Medical school final examination
Decreased salivary IgA	Academic striving
Increased antibody titres to herpes viruses	Medical school final examination

From McEwen et al. (1997b); see their Table 2 for list of references

In rats, pain-associated stressors decrease the activity of natural killer (NK) cells which is followed by increased probability of developing tumours (see Andersen et al. 1994 for a brief review). Corticosteroids and catecholamines mediate a decrease in immunocompetence following a situation of stress due to overcrowding; this, in turn, increases infection rates by microorganisms and susceptibility to developing cancer in rodents (Cassel 1974).

One important finding so far is that chronic stress can especially affect the onset and progression of haematopoietic cancers such as leukaemia (Lamkin et al. 2012, see also Cole and Sood's 2012 work quoted above). Stress can decrease the reproductive capacity of lymphocytes, especially B and T cells, suppressor/cytotoxic T cells, helper T cells and large granular lymphocytes, and it also decreases the activity of natural killer cells (Adler and Matthews 1994). As a result of sustained immunodeficiency due to social stress, some individuals may develop various forms of cancer in rodent models (see review in Azpiroz et al. 2003). Social stress could potentially also enhance ascitic (i.e. fluid-producing) Ehrlich tumour growth in mice (Morgulis et al. 2004). Stressors such as disorientating the individual in space, physical restraint, maternal deprivation and others that have been used experimentally in rodents may result in enhanced carcinoma growth and metastasis (see McEwen et al. 1997a, b and references therein).

In the study of stress, we should distinguish the *individual* and the *social* levels of analysis (e.g. Adler and Matthews 1994). In animal models, aggressive interactions involved in the establishment and maintenance of dominance hierarchies between members of a social group can be associated with stress, especially for the subordinate individual (but sometimes also for the dominant). Such stress is in turn the cause of a decrease in humoral immune capabilities (Azpiroz et al. 2003). Cellular immunity may also decrease in stressed individuals (e.g. subordinates), but not all types of immune cells may respond in the same manner. For instance the proliferative capacity of splenic cells may be depressed in subordinate individuals, but granulocytes and neutrophils may increase in numbers (Azpiroz et al. 2003). This means that social life, apart from its many potential benefits, may also have some negative effects on immunity and therefore the ability to resist disease in some

individuals. This is expected when social interactions are unstable and mainly stressful. The situation is reverted when social interactions are stable and reflective of cooperation and support between the members of a group.

The subtle complexity of the interaction between sociality and health is seen in that although social support tends to protect the individual from stressors and diminish their effects on the onset of disease and, conversely, social isolation favours the onset of disease, this is variable from species to species. In fact, social isolation in mice is initially stressful and results in decreased B and T lymphocyte immune responses, but as isolation becomes more prolonged it increases immunocompetence (Hilakivi-Clarke et al. 1993 and references therein). Such an effect of the length of time of isolation on immunocompetence is reflected in tumour growth: growth increases in mice isolated for short periods, but it decreases in mice isolated for longer periods (see Hilakivi-Clarke et al. 1993 for a review). Presumably, once the individual overcomes the initial stress of social isolation, it may enjoy the beneficial effects of living on its own such as avoidance of competition for food and shelter and the stress associated with aggressive interactions. This effect, however, may not be applicable to all social animals or at least not to all social conditions. In many humans, for instance, long-term social isolation may be detrimental to health and be a risk factor in disease development (see Spiegel and Kato 1996 for a review). On the other hand, living conditions of social overcrowding, especially if associated with poverty, are also linked with decreased probability of survival, including survival of cancer patients (see Savage et al. 1984 for the case of multiple myeloma). That is, in humans there seems to be a situation where extreme social conditions of either isolation or overcrowding may negatively affect immunocompetence and therefore increase susceptibility to disease, presumably through links with stress, among other factors. Ultimately, the precise effect of sociality on immunity and health will depend on the individual and what kind of specific interactions that individual establishes with others and the material resources available: sociality may be beneficial to the activity of the immune system if it leads to social support, reassurance and greater ability to acquire resources such as food and shelter; it may be detrimental to immunity if it is associated with stress and increased competition for scarce resources.

One of the central issues in the empirical testing of the association between psychological stress (and also depression) and cancer is the control of confounding variables, especially when large population-based datasets are analysed. Bernard Fox mentions how stress can have inhibiting or facilitating effects on tumours depending on their molecular and cellular causes: stress seems to inhibit viral tumours, whereas it enhances the carcinogenic properties of environmental chemicals in animal models (Fox 1995, see also Justice 1985). Regarding social effects, Brawley (2002) highlighted the effects of socioeconomic status on cancer risk, an issue also emphasised by Harold Freeman (1991, 2004) who reported evidence indicating that the poor in the USA have an increased incidence of cancer and 5-year survival rates that are 10–15 % lower than those in the rest of the population. Elias et al. (2005, see also Elias et al. 2004) described an association between severe exposure to the Dutch famine of 1944–1945 and increased probability of developing breast cancer in women. However Fox (1983 and references therein) also reports of no significant effects of the experience of prisoners of war and of survivors of

Table 2.5 Summary of the neurophysiological differences between proactive and reactive rodents in response to stressful conditions

Physiological and neuroendocrine characteristics	Proactive	Reactive
HPA axis activity	Low	Normal
HPA axis reactivity	Low	High
Sympathetic reactivity	High	Low
Parasympathetic reactivity	Low	High
Testosterone activity	High	Low

HPA axis hypothalamo-pituitary-adrenal axis
Modified from Koolhaas et al. (1999); see original table for list of references

concentration camps on subsequent development of cancer. Fox (1995) also mentions that there is little convincing evidence that bereavement may enhance the onset of cancer. More recently, Heikkilä et al. (2013) did not find evidence for job-related stress (job strain) to be associated with cancer risk in a meta-analysis of 12 European cohort studies involving 116,056 men and women.

Therefore, although there are molecular mechanisms that link chronic psychological stress and development of cancer, and there are population data that are consistent with this possibility, not all stressful situations have been shown to favour cancer development in population studies. In particular, we see next how coping strategies may be adopted that have the capacity to dampen the effects of stress on cancer.

Behaviour and Cancer Prevention/Suppression

In the previous sections we have emphasised the links between stress, hormones, immunity, behaviour and promotion of cancer at different levels of analysis. Turning the issue around, we may also ask whether there are molecular and physiological mechanisms that link behaviour with suppression of cancer. Would positive emotions such as affection, positive behaviours such as humour and laughter and an optimistic personality, for example, actually prevent the onset of cancer or perhaps help in suppressing its further progression? Although proper experimental work in this area is only now being undertaken, the results so far are encouraging.

Animals have evolved many strategies to withstand the health-damaging effects of stress, including behavioural coping strategies. In general, health is easier to maintain whenever the animal can predict and control the stressor (*escapable stressor*). If, on the other hand, the animal is incapable of coping with stress (as when the action of the stressor is *inescapable*) then negative effects on health are expected (Hilakivi-Clarke et al. 1993; Koolhaas et al. 1999). Animals can display various coping styles: the *proactive style* or *fight-flight* response may involve a degree of aggression from the part of the individual under stress, whereas the *reactive style* or *conservation-withdrawal* response involves less aggression and activity (Koolhaas et al. 1999). Table 2.5 shows some neurophysiological differences between proactive and reactive coping styles in rodents, with the hypothalamo-pituitary-adrenal axis being less active/reactive and circulating levels of testosterone being higher in individuals adopting the

proactive style, whereas reactive individuals have less circulating testosterone and higher reactivity of the hypothalamo-pituitary-adrenal axis. Reactivity of the components of the peripheral nervous system (sympathetic and parasympathetic) also differs between the two coping styles.

In animal models individuals adopting the proactive coping style are more susceptible to develop a cardiovascular pathology under stress but less susceptible to develop ulcers provided that they are capable of avoiding the source of stress. If such avoidance is impossible, then the proactive individuals are more likely to develop ulcers (Koolhaas et al. 1999). With time, ulcerative damage may potentially lead to cancer development (e.g. Dunham 1972). Proactive individuals are also more likely to develop *behavioural stereotypies* (repetitive patterns of behaviour) under stress, and stereotypies are associated with fewer ulcers. In both rats and pigs the proactive coping strategy is associated with greater cell-mediated immunocompetence and therefore enhanced resistance to infectious disease (Koolhaas et al. 1999). In humans, such diversity of coping styles may also characterise various personalities.

Few behaviours are more readily associated with coping in the face of stress than humour and laughter. Hayashi et al. (2006) carried out a study of gene expression during two contrasting experiences: one that elicited laughter (a comic film) and one that did not (a “monotonous academic lecture devoid of humour”, boring lecturers take notice). A total of 12 individuals (nine men and three women) participated in the study. The authors monitored the expression of 18,716 genes, and of those, 23 genes displayed significant changes in levels of expression between the humorous and humourless experiences. Products are known for 18 of those genes, and among those genes that were upregulated by laughter there is at least one that is relevant in the context of protection against cancer: *BCL2/adenovirus E1B 19 kDa interacting protein 3-like*; this gene has a functional role in apoptosis.

Dispositional positive affect, that is characterised by moods of happiness, relaxation and feeling pleased, has been associated with better immunocompetence. For instance, Marsland et al. (2006) studied the antibody response to vaccination with 20 µg doses of recombinant hepatitis B vaccine in 81 male and female participants in a study carried out in the USA. Greater *positive affect* was associated with a more elevated antibody response following vaccination. Similar results have been obtained more recently by Matsunaga et al. (2008) in Japan. They asked 12 male participants to watch a film feature that was either attractive (films featuring famous actresses) or not so attractive (an old weather report). Both a PET scan and a blood sample were taken while participants were watching the film. Watching the attractive film was associated with elevated circulating levels of natural killer cells and dopamine compared to controls, whereas the following brain areas were specifically activated: medial prefrontal cortex, hypothalamus, posterior cingulate cortex and cerebellum among others.

Therefore, whether through regulation of apoptosis, modulation of the immune system or other means, behaviours and states of mind that could be broadly described as “positive” have the potential to interfere with cancer. This is a fascinating area of research that fully deserves to be developed following the best scientific protocols available. We will return to this important topic in several of the remaining chapters.

To recap: the *sickness syndrome* characterised by a series of behaviours adopted by animals whose health is compromised, including animals suffering from various

forms of cancer is, at least in the initial stages of disease, an organised strategy evolved to counteract the debilitating effects of the disease itself. The sickness syndrome is the result of interactions between the nervous, immune and endocrine systems, with such inter-systemic communication being facilitated by molecules such as the cytokines. The link between immunity, hormones (such as steroids and catecholamines), sickness behaviour and cancer can be exemplified in the case of stress, psychological stress in particular, and the depressive mental state that it may lead the patient into. Specific molecular mechanisms that link behaviour and the onset and reproduction of cancerous mutant cells include production of ROS, alteration of telomere length, modification of apoptosis, DNA methylation and interference with immune activity, including both immune suppression and chronic inflammation effects. However, behaviour could also be linked to mechanisms that decrease the probability of cancer development.

In the next section we describe and comment upon some basic aspects of the relationship between cancer and behaviour in humans. The section serves as a broad introduction to the major themes of human behavioural oncology that will be developed in more detail in the rest of the book.

Cancer and Human Behaviour

The many interrelations between cancer and human behaviour are currently studied within the scientific discipline of behavioural oncology, also known as psycho-oncology (Holland et al. 2010). A discipline that although has roots extending back to the 1970s it became better established since the 1980s (Holland 2002). The need for such a discipline has emerged from changes in attitudes amongst both patients and their families as well as in the community of health practitioners (doctors, nurses), regarding the importance of the psychological dimension in the prevention, diagnosis and treatment of cancer and also in the return of cancer survivors to normal life. In an early review of the developments in this field, Dolbeault et al. (1999: 1556) remarked that the need for a behavioural oncological discipline springs at least in part from:

the shifting of attitudes away from fatalism about cancer; the more open disclosure of the diagnosis and, therefore, more open discussion with others; greater dialogue between doctor and patient; discussion with the patient about treatment options and asking for their participation in decision making; the ability to study scientifically the psychosocial domain due to the development of valid assessment tools; and the recognition that cancer prevention and screening depends in large measure on changing behaviours and attitudes.

Indeed, Satin et al. (2009) mention that about 85 % of cancer patients and also about 71 % of oncologists believe that cancer progression is somewhat affected by psychological variables.

Behavioural oncology aims not only to achieve an understanding of the interactions between cancer and behaviour but also to obtain better medical outcomes for the patient, such as increased survival rate and also increased quality of life; the

latter should be simply understood as the ability to function in life after having experienced cancer.

But before we introduce some of the major issues in human behavioural oncology, a few methodological considerations are in order. As we review the results of observations and experiments available in the specialised literature, care will be taken to keep the specific methodological limitations of those studies in mind, as such limitations establish an upper boundary for the reliability of our interpretations and inferences. The quality of knowledge about psychological aspects of cancer is obviously constrained by the quality of the research tools used to produce such knowledge. Inferences drawn from poorly designed studies, with small sample sizes and uncontrolled confounding variables, should be taken with a pinch or two of salt (Fox 1995), as they may confound the correct causative relationship between factors: what is a direct cause, what is an indirect cause (e.g. smoking behaviour causes cancer not because of the behaviour as such but because of the carcinogenic compounds present in tobacco) and what is a consequence (behaviour may potentially affect the onset and/or progression of cancer or vice versa) (Fox 1995).

In spite of those obvious limitations, small-scale studies may still be useful, especially when they show interesting or unexpected patterns that may inspire new directions in research; but they nonetheless must be followed up by larger scale and better designed studies that will provide more reliable tests of whatever hypothesis we want to investigate. In particular, *prospective* studies that involve the follow-up of control and experimental patient populations for variable periods of time are the best way to investigate the effects of behaviour on cancer development and progression and then the effects of therapies on behaviour and functioning. These studies should be structured as randomised control trials that include information collected at baseline and then over a variable period thereafter. If the effectiveness of a psychological intervention is being tested (e.g. meditation therapy), biological and psychological variables should be recorded pre-intervention (baseline) and then post-intervention (see Hawkins 2001 for a critique of such methodological issues). In prospective studies sometimes a single, large population of individuals is followed up and then comparisons made between the sub-population that develops cancer at some stage into the future and the sub-population that remains healthy (control). Alternatively, studies may use a *retrospective* approach, in which patients are interviewed for the first time after they have developed cancer and asked to recall past events. The same questions are asked to a control sample of healthy individuals for comparison. Although retrospective studies are useful as a research tool, the prospective method is clearly far superior as it is less susceptible to memory failures from the part of the patient, and therefore it should be preferred.

Some of the published studies are opportunistic, reporting information gathered from any patient who was available at the time; such studies should be regarded as being merely exploratory. Another common feature of studies in behavioural oncology is the reliance on the use of questionnaires and sometimes interviews. Most authors use research instruments based on some form of questionnaire/s, but such instruments should be validated to ensure that they are actually measuring what they are supposed to measure, before they can be trusted for broader use.

In addition, although both questionnaires and interviews do provide a window into the behaviour and mental processes of the patient, they should be supplemented with more “naturalistic” observations along the ethnological tradition. Language is a double-edged sword: it can be used to inform or to deceive (even self-deceive). Thus some researchers record the totality of communicative interactions during a specific time span and then use linguistic tools such as discourse analysis to achieve a more complete understanding of what patients and others are communicating with their choice of words.

In addition, some aspects of behavioural oncology are more amenable than others to be studied through controlled experiments; such is the case of sensory perception and cognitive abilities for instance. If controlled experiments are possible—both practically and ethically—they should be carried out. Although in this book we will mention and comment upon relevant results from all kinds of studies, the reader will keep in mind that some of those results will be methodologically more reliable than others.

Throughout this book we will also review many works that use a meta-analytical approach. Meta-analyses are statistical tests of hypotheses based on the results of a number of independent studies, usually accessed through a literature search via electronic databases such as Psycinfo, Web of Science, Medline and Scisearch. The objective of a meta-analysis is to evaluate the standing of a hypothesis using the empirical results obtained by independent researchers. A hypothesis increases in strength the more consistently positive the results of many independent tests have been. On the other hand, if the results of such tests tend to be negative, the hypothesis can be finally rejected (falsified). Although meta-analytical techniques are extremely useful tools, works using meta-analyses have been criticised as “garbage in and garbage out wrapped up in fancy statistics”. We agree that if the empirical works that are the source of data for a meta-analysis are poor and unreliable, or the sample is biased, then the meta-analysis is of little value. But this is not always the case, and in fact a common approach in meta-analyses is to start with a large sample of articles that are subsequently screened for quality, and more often than not the original large sample is drastically reduced to only include those articles that together form a reliable sample, relatively homogeneous in methodology and kind of participants (e.g. sex ratio, age distribution of patients, sample size). In these studies, the specific statistics used should also be justified.

As far as the links between psychology and cancer are concerned, they can go in two possible directions: cancer may affect behaviour, and, conversely, behaviour may potentially affect the onset and/or progression of cancer. Of course, there is also the possibility that some aspects of cancer may have no manifest effect on behaviour and, vice versa, some behavioural factors may not affect the disease. One important issue that should also be considered when studying the relationship between cancer and behaviour is to what extent anti-cancer therapy itself (surgery, chemotherapy, radiotherapy, immunotherapy, hormone therapy) may directly cause behavioural changes in patients (see for instance Andersen et al. 1994).

Finally, we should also explain two basic concepts in medicine that are sometimes confused in lay language: *illness* and *disease*. Following Eisenberg (1977, see also Posner 1991), illness could be defined as “experiences of devalued changes in

states of being and social function”, whereas disease could be defined as “abnormalities in the function and/or structure of body organs and systems”. Thus disease is mainly defined in medical physiological terms, whereas illness expresses the experience of disease as it is subjectively understood by the patient.

Broadly speaking, the medical and human experience of cancer patients goes through various phases during the course of the disease. Each one of those phases is characterised by particular states of mind that are affected by the type of cancer, medical procedures and therapies. The personal characteristics of the patients and their sociocultural conceptualisation of the disease also play a role in their state of mind. Similarly, the multiple interactions that they develop in medical settings with the oncological team of doctors and nurses, and ordinary exchanges with relatives, acquaintances and other members of their social milieu, are also vitally important. Those phases are mainly dictated by the causative sequence of the disease, its impact on behaviour and also the learned and socially structured procedures of seeking and delivering medical care. Five, and in some cases six, major phases could be described throughout the patient’s experience (see Coyle and Foley 1985; Baum and Posluszny 1999; Rossi Ferrario et al. 2003):

1. The experience of disease starts with an initial perception of change in the usual patterns of health—things are not “business as usual”—that may (or may not) lead the individual to seek medical advice. Seeking (or not) such medical advice may be a purely personal decision or it may be a decision influenced by members of the individual’s social entourage.
2. In the medical encounter the patient and the doctor establish a communicative interaction that may lead to a request for specific medical exams and subsequent discussion of the results of such tests. This hopefully conduces to a diagnosis or an establishment of the kind of disease that is affecting the patient.
3. Treatment follows the diagnosis, and a prognosis, or judgment on the probable course of the disease, including judgment on the probability of recovery based on past knowledge and current personal situation of the patient, is produced. At this stage, the patient is expected to adhere to the prescribed treatment, but use of complementary therapies may also be sought by some patients following personal convictions, beliefs and consideration of specific professional or non-professional advice.
4. From then on the patient may continue with regular follow-up visits for a period of time until he or she is granted remission, a stage that is broadly characterised by a state of hope from the part of the patient. Some preventative recommendations may also be made at this stage on the basis of the available medical knowledge to decrease the probability of relapse.
5. Prevention notwithstanding, it is also possible that the disease may indeed recur at some point into the future, in which case the process starts all over again, usually associated, at the very least, with a degree of disillusion from the part of the patient.
6. In the most extreme of cases the progression of the disease—whether in its initial manifestation or after it has recurred—may lead to an end-of-life process that may involve specific behaviours, perceptions, thoughts and emotions in patients and family and the offering of palliative care from health practitioners.

As we have seen, one of the first consequences of having cancer is the experience of stress that involves various interactions between the immune, endocrine and nervous systems. The stress response is initially an adaptive syndrome (acute stress response), but it may potentially become part of the problem once stress becomes chronic and the disease also reaches the stage of overwhelming the biological abilities of the organism to protect itself (Kiecolt-Glaser et al. 1993; Andersen et al. 1994). As the abilities of the individual to withstand the effects of the disease decrease, he or she may experience a psychological state of distress that could affect the ways in which the person interacts with his/her surroundings (see for instance Fylan 1998; Ohaeri et al. 1998). In some cases distress may potentially progress into a state of depression.

Although an individual may develop depression or not as a result of specific stressful life experiences, when it does happen, depression may be mild or deep, or it may be of brief duration or long-lasting depending on the capacity of the individual to cope. Depression itself may also aggravate the effects of disease in the case of cancer patients, and therefore it is not surprising that coping mechanisms have evolved to counteract the effects of depression (see Baum and Posluszny 1999 for a review).

At the individual level, coping with depression may be affected by nutrition for instance, and so a specific diet may help in this task. Exercise may also protect against the effects of chronic stress and depression (Andersen et al. 1994). Personality traits like the tendency to resort to denial may be an additional effective coping strategy (at least in the short term and provided that it does not delay medical intervention too much). Whenever individual coping mechanisms are insufficient, social support may provide the much required help. Various forms of psychotherapy have also been used to aid the coping process of cancer patients, but more commonly it is the day-to-day social environment of the patient that could make a difference to the cancer sufferer (see Gil et al. 1987; Hilakivi-Clarke et al. 1993; Andersen et al. 1994 for reviews).

Three major models have been proposed to explain the role of social support in coping with cancer: The *stress buffering model* that points to the role of social support in protecting the patient from experiencing stress in the first place; the *main effect model* that emphasises the beneficial effects of social support in slowing down the stressful consequences of the disease and, potentially, the progression of the disease itself (Spiegel and Kato 1996); and the *social comparison model* (Festinger 1954) which points to the effects that others' behaviour may have on the coping decisions of a patient. The three models will be analysed more thoroughly in Chap. 5. In humans, social support may be a significant aid to coping with cancer, although the coping effects of social support are variable according to individual characteristics. Cassel (1974) points to the importance of maintaining stable and reliable supportive social links but also to the potentially negative impact of stress associated with social subordination and discrimination.

Apart from *denial* that we mentioned above—and the more basic *fight-flight* and *conservation-withdrawal* responses—other aspects of personality may also affect the perception of stress and the ability to cope with it. Two broad aspects of personality have been identified in humans that lay at the extremes of a continuous scale from proactive to passive attitudes towards the disease: *fighting spirit* and *type C personality*.

Table 2.6 Distribution of psychological response to diagnosis of cancer (PRD) in breast cancer and lymphoma patients

PRD	Breast cancer	Lymphoma
Denial	16 (18%)	18 (36 %)
Fighting spirit	13 (15 %)	6 (12 %)
Anxious/preoccupation	32 (36 %)	14 (28 %)
Stoic acceptance	23 (26 %)	9 (18 %)
Helpless/hopeless	4 (5 %)	3 (6 %)
Total	88	50

Adapted from Morris et al. (1992)

A person with a fighting spirit is characterised by “optimism, assertiveness and determination” in the fight against cancer, whereas a type C personality is “conforming and acquiescent; they tend to respond to stress with depression, helplessness, and hopelessness” (Spiegel and Kato 1996: 14). Broadly speaking, there is a tendency for fighting spirit personalities to be better able to survive cancer than type C personalities, and they also tend to better adhere to the prescribed cancer treatment (Ayres et al. 1994). But, admittedly, research in the area of cancer and personality faces various methodological difficulties associated with control of confounding variables.

In a classic prospective study of non-metastatic breast cancer patients, Steven Greer and collaborators showed that those who were more likely to be alive 5 and 10 years post treatment had mainly responded to their condition with either “positive avoidance/denial” or “fighting spirit”, whereas patients responding with a “fatalistic or helpless” attitude were less likely to be alive (Greer et al. 1979; Pettingale et al. 1985). The pattern remained the same over a 15-year period of follow-up (Greer et al. 1990). Tina Morris and Keith Pettingale repeated the prospective study on a different group of women with breast cancer, but this time they also included a group of women and also men with lymphoma for comparison (Morris et al. 1992). Their results suggest that individuals who saw cancer as “a severe threat to all aspects of life” at diagnosis had a significantly lower survival (42 months) than those who did not have the same attitude (>60 months). On average, the lower survival subjects also showed elevated levels of depression. Although the female breast cancer patients who died by the end of the 5-year period of this study also provided a larger number of “confronting responses”, in the case of male lymphoma patients those who died tended to show higher “suppression of anger” and a more fatalistic or helpless attitude. Male patients also tended not to seek information and maintained themselves busy as a strategy to avoid thinking about their condition (Morris et al. 1992). This high level of denial in this sample of male patients may perhaps explain, at least in part, the behavioural differences shown in Table 2.6 between breast cancer patients (women only) and lymphoma patients (both women and men), where the percentage of lymphoma patients showing “denial” is larger (36 %) than among breast cancer patients (18 %). Interestingly, “denial” is a concept borrowed from psychoanalysis (Vos and de Haes 2007), but whereas psychoanalysis sees it as an expression of mental pathology (which in some extreme cases may indeed occur, Massie and Holland 1992), in behavioural oncology it can also be seen as a short-term coping strategy, a view that is also in accordance with modern evolutionary medicine.

Table 2.7 Effects of gender, age and ethnic background on cancer denial

Gender	M > F (3)		M < F (1)		
Age	Y > E (1)		Y < E (5)		
Ethnic background	Belgians vs. Turkish	Asians vs. Caucasians	“Blacks” vs. “Whites”	Hispanics vs. non-Hispanics	Australian born vs. non-Australian born
DD	B < T	A > C			
DI	B < T	A < C		H > NH	AB < NAB
DA	B > T		B > W		
BE			B < W		

Numbers in parenthesis for the categories of gender and age are frequencies

M male, *F* female, *Y* young, *E* elderly, *DD* denial of diagnosis, *DI* denial of impact, *DA* denial of affect, *BE* behavioural escape

Adapted from Vos and de Haes (2007)

Table 2.7 shows some effects of gender, age and ethnic background on denial in cancer patients. Denial tends to be adopted slightly more often by males and the elderly, whereas various forms of denial may be affected by ethnic background. In fact, as far as ethnicity is concerned, denial, and presumably other psychological variables as well, should be classified in a more sophisticated manner to account for their diversity of expression. By doing so we may uncover a degree of ethnic variability that is far more informative. For instance, although a Belgian sample seems to display lower levels of denial of diagnosis and of impact, they display higher levels of denial of affect than a Turkish sample of patients (Table 2.7). Moreover, even when we can subcategorise a concept such as denial, the possibility still remains open that different ethnic groups may not share the same conceptualisation of the term and its variants. In brief, they may interpret and understand denial—or any other term—differently. This means that cross-cultural studies cannot be carried out without a deep understanding of each one of the different cultures involved (Sharifian 2003; Cordella 2011a). We will return to the issue of denial in various chapters of the book, and we will focus on cross-cultural aspects of behavioural oncology especially in Chap. 6.

Behavioural patterns may also be associated with various prognostic factors and therefore cancer progression. This issue has been recently reviewed by Lutgendorf and Sood (2011). Among breast cancer patients, fewer (60 %) of those showing “denial and a fighting spirit” were diagnosed with a grade 2 tumour (or higher) compared with patients showing “anxious/preoccupation, stoic acceptance and helpless/hopeless” (76 %) (Morris et al. 1992). The same pattern is maintained for the percentage of patients undergoing a more radical operation (28 % of those in the “denial and a fighting spirit” category vs. 49 % of those in the “anxious/preoccupation, stoic acceptance and helpless/hopeless” category). Interestingly, a different pattern was found for lymphoma patients. In this case “denial and a fighting spirit” were associated with tumour grade 2 or more in 54 % of patients, whereas “anxious/preoccupation, stoic acceptance and helpless/hopeless” were associated with such tumours in 46 % of patients; but this result may be an effect of sex in the lymphoma

group, as only 58 % of males displayed the latter response, whereas 83 % displayed “denial and a fighting spirit”. These associations between personality traits and disease progression are consistent with the patterns of deaths: patients displaying “stoic acceptance” comprised 66.6 % of all deaths, whereas patients displaying “denial and fighting spirit” comprised 57.8 % of those who were still alive and showed no recurrence of breast cancer (Pettingale et al. 1985).

Mulder et al. (1992), in their review of the association between psychosocial factors and progression of breast cancer, showed a relationship between increased cancer progression and the experience of sustained stress. They also pointed out that decreased progression is associated with a fighting spirit, increased attitude of denial, less feelings of hopelessness, more extroversion and more joy (see Table 2.8 and also Hilakivi-Clarke et al. 1993).

However it should also be pointed out that some of the studies reviewed in Mulder et al.’s work did not find statistically significant associations between cancer progression and psychosocial variables (Table 2.8).

If personality and other psychological traits can affect cancer progression then it is possible that they can also be associated with diverse probabilities of survival (see Pettingale et al.’s 1985 work quoted above). In a 5-year-long prospective study of a cohort of 578 women with early-stage breast cancer, Watson et al. (1999) found that, by the end of their study, most patients were alive (with no sign of cancer recurrence) than dead, with the exception of the very high depression category, whereas many women were alive with no recurrence (50 %) as they were dead. Those patients who were alive with no recurrence of cancer mainly displayed a “fighting spirit”, the lowest levels of anxiety and low-to-medium levels of depression. On the other hand, patients who were alive but had a recurrence of cancer tended to show more helplessness/hopelessness, levels of anxiety that tended to be low and levels of depression that also tended to be low, the last two trends being only slight. Finally, patients who by the end of the 5-year period had died were characterised by anxious “preoccupation” and “fatalism”, and they also tended to display high levels of anxiety and very high levels of depression (see Table 2.9).

In spite of the available results indicating the effects of psychological factors on cancer onset and/or progression, caution must be exerted to avoid the potential negative effects that false expectations may have on the psychology of cancer patients and their ability to cope emotionally with their illness (Garssen 2004). After reviewing 70 prospective cancer studies Bert Garssen rightly pointed out that not all types of cancer are necessarily expected to be equally susceptible to psychological factors, simply because the relationship between psychology and cancer must be mediated by molecular mechanisms and not all molecular alterations associated with behavioural changes would be able to equally affect all types of cancer. Vice versa, not all types of cancer will be associated with molecular and physiological changes that will affect behaviour in the same way. Broadly, Garssen shows that the sample of prospective studies published between 1978 and 2002 that he reviewed indicate a variable effect of psychological factors on the onset and progression of various types of cancer that varies between 64 and 100 %, although the effect of psychological factors on cancer progression is usually more commonly detected in such studies

Table 2.8 Psychosocial variables associated with breast cancer progression

Reference	N	Psychosocial variables	Direction of association between psychosocial factor and progression
Funch and Marshall 1983	83	Life events, social support	Life events Stressful life events and social support are negatively correlated with survival Increase of relative risk of recurrence after severe life event Life events and low social class were associated with faster progression Social support
Ramirez et al. 1989	50	Life events	
Forsén 1991	87	Life events, social class	
Neale et al. 1986	1,261	Marital status	Social support Widowed patients were less likely to survive than married patients No differences in survival between married and unmarried women More social support was related to longer survival Mental traits
Goodwin et al. 1987	25,706	Marital status	
Waxler-Morrison et al. 1991	133	Social support	
Greer et al. 1979, 1990	69	Denial, fighting spirit, stoic acceptance, helplessness/hopelessness, hostility, extroversion	Patients who scored higher on fighting spirit and denial lived longer Patients scoring in the middle third of the hopelessness scale had longer remissions
Cassileth et al. 1988	88	Social relationships, job satisfaction, use of psychotropic drugs, life satisfaction, subjective view of adult health, hopelessness/helplessness	
Derogatis et al. 1979	35	Affect balance scale, adjustment to illness, attitude towards illness	
Jensen 1987	86	Repressive defensiveness, self-deception	Long-term survivors were more distressed overall and showed more expression of negative emotions Good prognosis was associated with expression of negative affect and with the absence of helplessness/hopelessness
Hislop et al. 1987	133	Self-esteem, psychiatric symptoms, extroversion/neuroticism, coping	
Levy et al. 1988	36	Affect balance scale	
Dean and Surtrees 1989	122	Fighting spirit, denial, stoic acceptance, anxiety, depressed mood	Expressive activities at home, extroversion, and low anger level were prognostic factors for survival Patients who expressed more joy at baseline lived longer Women with a psychiatric diagnosis before operation and high denial after operation show less recurrence No associations
Cassileth et al. 1985	60	Social support, marital history, job satisfaction, life satisfaction, hopelessness/helplessness, adjustment to cancer	
Jamison et al. 1987	46	Anxiety, general well-being, self-esteem, hostility, depression	
Spiegel et al. 1989	86	Self-esteem, coping, phobias, denial	No consistent differences between short and long-term survivors No correlations with survival No correlation with death or occurrence of metastases No association with occurrence of metastases
Buddeberg et al. 1991	107	Depressive coping, self-encouragement/distraction	
Barracough et al. 1992	204	Social difficulties, depressive illness, lack of confiding relationships	

Adapted, with reference corrections, from Mulder et al. (1992)

Table 2.9 Behavioural and medical outcome of breast cancer patients over 5 years

	Alive with no recurrence (N=395)	Alive with recurrence (N=50)	Dead (N=133)	Total (N=578)
Predominant response				
None	37 (74 %)	3 (6 %)	10 (20 %)	50
Fighting spirit	117 (70 %)	14 (8 %)	35 (21 %)	166
Helplessness/hopelessness	82 (65 %)	16 (13 %)	29 (23 %)	127
Anxious preoccupation	81 (68 %)	9 (8 %)	30 (25 %)	120
Fatalism	64 (65 %)	8 (8 %)	27 (27 %)	99
Unknown	14 (88 %)	0	2 (13 %)	16
Anxiety				
0–7	283 (70 %)	39 (9 %)	86 (21 %)	407
8–10	67 (66 %)	8 (8 %)	27 (27 %)	102
≥11	44 (65 %)	4 (6 %)	20 (29 %)	68
Unknown	1	0	0	1
Depression				
0–7	370 (68 %)	48 (9 %)	123 (23 %)	541
8–10	20 (74 %)	2 (7 %)	5 (19 %)	27
≥11	5 (50 %)	0	5 (50 %)	10

From Watson et al. (1999)

than effects on cancer initiation. On the other hand, many studies also tend to find no association between cancer and psychology.

In his conclusion, Garssen (2004: 331–332) states that:

We consider repression of negative emotions, denial/minimizing the impact of the disease, and helplessness as ‘*promising*’ risk factors for cancer progression, although their effect has not been confirmed in all studies. Some indications were found for a role of social support, loss events, and marital status. However, the role of life events (in general), distress, having psychological problems or a psychiatric diagnosis, fighting spirit, stoic acceptance/fatalism, active coping, personality factors in general, and locus of control in particular, is *doubtful*. (italics ours)

We simply regard this conclusion as a cry for more and better research in behavioural oncology that will hopefully clear up the mist surrounding those factors that may be “promising” and also those that currently seem to be “doubtful”.

In sum, the cancer patient goes through a series of phases in his/her experience that from the initial diagnosis hopefully leads to remission. In each one of those phases, issues of feelings, thoughts and communication can be important in understanding both the progression of the disease and the ability of the patient to either fight back or better adapt. The feeling of distress is clearly one of the first emotions experienced by the patient, and the ability to activate coping strategies may allow the patient to withstand the effects of such psychological stress.

In the next section we focus more specifically on one of the most basic sensations associated with many forms of cancer and their treatment: pain.

Disease and Pain

Cancer is often associated with pain, and we have seen earlier in this chapter that increased sensitivity to pain is an adaptive aspect of the sickness syndrome. Most people have an intuitive understanding of the meaning of the word “pain” and what it involves in terms of personal experiences and feelings, although exceptions do exist as in the case of sufferers of *familial dysautonomia* (or *Riley–Day syndrome*) who have a congenital inability to feel pain. But beyond our intuitive understanding of pain, a formal definition is also required in a technical book like this. The *International Association for the Study of Pain* defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (IASP Subcommittee on Taxonomy 1979, quoted in Coyle and Foley 1985: 93). Pain is experienced by about 14–50 % of patients just diagnosed with cancer and by between 50 and 95 % of patients going through advanced (e.g. metastatic) phases of cancer (Ahles et al. 1983, 1984; Elliott et al. 1996; Sela et al. 2002; McGuire 2004; Jacobsen et al. 2009). The various types of cancer are also associated with different pain experiences, with lymphoma patients usually reporting among the lowest levels of pain, whereas patients with metastatic cancer of the bones tend to report high levels of pain (Ahles et al. 1984).

Traditionally, pain was seen as a unidimensional phenomenon resulting from a functional link between peripheral pain receptors and specific brain centres. In 1965, however, Ronald Melzack and Patrick Wall proposed a new theory of pain: the *gate control theory* that incorporates other mechanisms apart from the neurosensory, such as the affective and also the cognitive. Such additional dimensions are associated with pain via interconnected neural networks in the central nervous system (see also Melzack 2008). Pain is therefore not a unidimensional but a multidimensional phenomenon. More specifically, Ahles et al. (1983, see also Weisenberg 1998) identify five major components of cancer pain, *physiological*, *sensory*, *behavioural*, *affective* and *cognitive*, to which McGuire (1987) added a sixth, the *sociocultural* (see Ahles and Martin 1992 for a review):

1. *Physiological*: This refers to a broad physiological component of cancer pain that derives from the action of the neuro-immune-endocrine system (what Ronald Melzack calls the “neuromatrix” (Melzack 1999)).
2. *Sensory*: This is a more specific component that determines the response to pain in association with the intensity of the stimulus and the specific tissues involved.
3. *Behavioural*: There is a behavioural and motivational component that is affected by both the direct neurological effects of pain on behaviour and pain as a stimulus releasing those behaviours that aim at controlling pain.
4. *Affective*: The affective or the emotional component involves the manifestation of depression and anxiety in response to pain.
5. *Cognitive*: A cognitive aspect can also be identified that refers to the ways in which the pain experience affects the patient’s thoughts.
6. *Sociocultural*: The sociocultural component is dependent on the cultural traditions concerning pain and the beliefs regarding its causes and management.

Below we comment in more detail on those components. In addition, cancer pain can be etiologically, that is, causatively, subdivided into three major categories: pain caused by direct effects of cancer (such as when the tumour infiltrates bone or nervous tissues), pain resulting from the medical procedures used in diagnosis and finally pain that is caused by the effects of cancer treatment (as in the case of some post-surgical and post-chemotherapy or radiotherapy syndromes) (McGuire 2004). Cancer pain may be acute, that is intense and short term, or chronic, that is noticeable and long term (see Coyle and Foley 1985 for a review). Chronic cancer pain may be a result of progression of the disease or it may also be a side effect of therapy. In addition, patients who suffer from cancer may have also had pre-existing chronic pain of a different origin compounding the painful effects of both cancer and cancer therapy. Finally, pain may become a central issue in the case of the cancer patient who is close to death: when end of life nears, most patients would hope for a quick, gentle and painless process.

Acute pain is clearly adaptive, serving “as a warning device, an alarm system activated in response to impending damage to the organism” (Scholz and Woolf 2002: 1062). Short-term nociceptive pain, caused by the stimulation of specialised nerve receptors by external stressors such as a flame or a block of ice, falls into this acute pain category. Pain can also be “inflammatory” that is caused by mediators of the inflammatory response such as the cytokines; and there is also a “neuropathic pain” which is a pathological and chronic form of pain (Scholz and Woolf 2002).

In general, we respond to acute pain with a degree of anxiety and by looking for a treatment that would abate or eliminate such pain. If pain persists, we respond by decreasing our level of activity, limiting social interactions and eating less, a response that is adaptive in terms of saving energy that can then be diverted to the healing process and decreasing further damage to the body by avoiding potential infections (Wall 1989; Wilkie et al. 1992). Such responses are also found in cases of pain experienced by cancer patients. However, the exact expression of emotions and behaviours during a painful experience will also be affected by the patient’s personality, with more extraverted patients being more likely to express their feelings of pain. Alternatively, the pain experience itself may increase extraversion and the patient’s willingness to express his/her feelings (Stiefel 1993).

Therefore, from a biological perspective pain, as it is experienced by cancer patients, is part of an internal mechanism of warning aimed at self-preservation, a function that would be expected from mechanisms selected throughout our evolution. However, one of the salient characteristics of the neurobiological system of pain perception is its plasticity, so much so that a painful sensation may be perceived even if no stimulus is present, or it may become associated with specific stimuli that do not usually trigger a pain response; or the pain response may become exaggerated with time, after repeated exposure to the same kind of stimulus, or have no functional adaptive effect on the organism depending on the stimulus. The individual may even become hypersensitive or hyposensitive to pain, thus changing the threshold level at which he or she perceives pain (Scholz and Woolf 2002). Such plasticity is also affected by the interaction of pain perception with other plastic faculties of

Table 2.10 Common psychological factors increasing the perception of pain

<i>Anxiety</i>
Fear of pain
Fear of loss of control
Fear of loss of mobility/independence
Fear of becoming a burden
Fear of abandonment
Fear of distorted body image
Fear of death
Financial worries
Uncertainty about the future
<i>Depression</i>
Sense of hopelessness/helplessness
Sense of aloneness despite friends
Sense of isolation
Sense of withdrawal by friends
Loss of role in family
Loss of job, prestige, income
<i>Anger</i>
Poor communication
Expectations from family, self and health providers not met
Lack of sense of urgency by health professionals
Nobody cares/understands
The unfairness of it all

From Coyle and Foley (1985)

our brain such as cognition (cognitive schemata, coping, see Porcelli et al. 2007). *Cognitive schemata* for instance are images of the salient characteristics of specific objects or events. This means that an event may or may not be perceived as painful according to the mental characteristics of the individual, not just the intensity of the event as it can be described through specific instrumental measurements. Given their plasticity, such cognitive mechanisms may also be activated in non-functional contexts, as in the case of exaggerated preoccupation with pain, potentially leading to psychological morbidity. In extreme cases pain sensations may be the only actual evidence available that anything may be wrong with the individual.

From a neurological perspective, it is known that acute pain mainly stimulates the following brain areas: thalamus, primary and secondary somatosensory cortices, anterior cingulate cortex and prefrontal and insular cortices (Apkarian et al. 2005). Not surprisingly, the same areas are also involved in the effect of various behaviours on the perception of pain. For instance, anticipation of pain is associated with the activation of the prefrontal and the anterior cingulate cortices (Apkarian et al. 2005).

The perception of pain may be modulated by various psychological factors, and some of the major factors that specifically increase the perception of pain are listed in Table 2.10. Such factors are associated with feelings of anger, anxiety and depression.

Indeed, pain is commonly associated with psychological distress and even depression in cancer patients (Massie and Holland 1992; Zaza and Baine 2002); and

once the patient is experiencing distress or depression it is also possible that pain may start to be experienced in new and unexpected locations in the body, a process known as *somatization*. As stated by Massie and Holland (1992: 101): “emotional states may represent both a consequence of and a contribution to pain in patients with cancer”.

Behaviours associated with pain may also have a social and cultural function. For instance some such behaviours such as grimacing, that are adopted during a painful experience, may serve to communicate to others that the individual is in trouble and requires aid (Wilkie et al. 1992; de Williams 2002 and references therein). However, in a study carried out in the USA on lung cancer patients (men and women), Diana Wilkie and collaborators found that the list of behaviours most used by cancer patients to try to control pain are those that are most likely to have a direct physiological effect on pain control, such as bracing, various forms of repositioning the body, massaging and pressuring the part of the body that is in pain (Wilkie et al. 1992). Participants in Wilkie et al.’s study stated that the behaviours performed did not have a function to inform others about their feeling pain. But communicating a state of pain could be achieved with any behaviour that is already known to be a sign of the individual discomfort, whenever that behaviour is performed in the presence of others. That is, communicating to others that one is in pain through the expression of specific behaviours or body postures that are routinely adopted in such a circumstance does not require intentionality. On the other hand, intentionality is certainly involved whenever individuals in pain try to hide their pain from others, in which case they may withdraw to a more private place whenever they feel the need to massage a body part in pain.

From a social perspective, behavioural expressions of mild and transient pain may help in recruiting aid, whether the person expressing pain consciously expects receiving help or not. However, the chance of receiving repeated assistance from individuals who are free to decide whether to help or not (e.g. strangers, acquaintances, but to some extent also family members) is also expected to decline in time as pain becomes chronic (Zaza and Baine 2002 and references therein). The situation is of course different in an institutional setting where the caregiver is under contractual obligation to provide aid. This is an important issue that impinges on the need to provide assistance and support to families who have the primary responsibility for the care of cancer patients suffering from chronic pain. External support may give a respite to relatives and help them endure the stress associated with long-term caring for a patient in such conditions.

On the other hand, cancer patients may also learn to modulate their expressions of pain in order to condition their caregivers, such as a spouse, with the objective of extracting a more intense or more continuous level of care (see Gil et al. 1987 and references therein): a behaviour that may stretch the endurance of the caregiver to its limits. One particularly well-studied aspect of this operant conditioning mechanism is a behavioural pattern known as *catastrophising*. Following Keefe et al. (2000, cited in Keefe et al. 2003) catastrophising can be defined as “an individual’s tendency to focus on and exaggerate the threat value of painful stimuli and negatively evaluate one’s own ability to deal with pain”. This behaviour seems to be far

more frequent than one may think, accounting for a range of between 7 and 31 % of the variance in the ratings of pain. Sullivan et al. (2001) have suggested that catastrophising is a coping strategy adopted by some individuals that is directed at seeking a relief from pain through requesting reassurance and support from others. For instance, levels of satisfaction with social support have been shown to be positively correlated with level of pain behaviour in some studies (Block et al. 1980; Gil et al. 1987). If the patient is catastrophising and the caregiver is unresponsive, the level of expressed pain may tend to decrease up to a point, whereas responsive caregivers will reinforce the behaviour. Of course, this operant conditioning mechanism for the attraction of social support does not necessarily apply to all cancer patients, but to some it may (see Weisenberg 1998).

Keefe et al. (2003) studied the interaction between 70 patients suffering from various forms of gastrointestinal cancers and their caregivers in the USA. They found that assistance received by the patients was positively correlated with their level of catastrophising. Moreover, caregivers who attended patients prone to catastrophising also suffered more stress. But more importantly, although caregivers did realise the potential for manipulation from the part of the catastrophising patient, and they responded by criticising such patients, they nevertheless did not withdraw help and support. Caregivers presumably realised that although the operant conditioning aspects of catastrophising is a real phenomenon, they were reluctant to follow this up with actual reduction of care, as the health costs of neglecting a real need for assistance may be much higher than the benefits of preventing the patient from manipulating his/her caregiver. Compounding this, in a professional context, doctors and nurses may also risk being subject to disciplinary or perhaps even legal action if the patient complains of neglect.

Issues of manipulation notwithstanding, in their review, Zaza and Baine (2002) concluded that out of the various behavioural strategies to cope with cancer pain that they listed, such as cognitive coping, catastrophising, diverting attention, reinterpreting pain sensations and others, the strongest association that they found was between increased levels of catastrophising and increased pain intensity. This suggests that overt expression of pain may usually be an honest signal. Moreover, some patients may even show the opposite pattern of suffering their pain in silence, as when they personally or culturally value *stoicism* (e.g. Chung et al. 2000).

The pain experience can also be modulated by aspects of personality. Porcelli et al. (2007) for instance studied both male and female patients with various forms of cancer. Pain was positively associated with poor adjustment to both the disease and the metastatic nature of cancer progression. In particular, patients not experiencing pain had higher levels of personality characteristics of “fighting spirit” and lower levels of “hopelessness–helplessness” as measured through the *Mental Adjustment to Cancer Scale* (MAC) (see Table 2.11) than patients experiencing pain. However, patients experiencing pain also had higher levels of conviction regarding their diseased status but lower ability to perceive actual symptoms of disease according to results from the *Illness Behaviour Questionnaire* (IBQ) (Table 2.11). This suggests that, to some extent, the perception of pain may be exaggerated in patients who are more convinced about being ill. Such patients also had

Table 2.11 Comparison of patients with and without pain

	Pain (<i>N</i> = 45)		No pain (<i>N</i> = 63)	
	Mean	SD	Mean	SD
MAC				
Fighting spirit	38.11	6.11	40.94	6.14*
Hopelessness/helplessness	12.89	3.23	11.33	3.26*
Anxious preoccupation	19.04	4.36	19.11	3.41
Fatalism	20.49	3.28	20.38	3.02
Avoidance	2.22	1.08	2.27	1.14
Overall adjustment to cancer	27.21	8.31	28.21	8.38
IBQ				
Hypochondriasis	3.22	1.58	3.02	1.70
Disease conviction	4.53	1.32	2.95	1.66**
Disease perception	1.27	0.99	1.90	0.82**
Inhibition	2.69	1.53	2.35	1.65
Dysphoria	2.78	1.46	2.21	1.52
Denial	3.11	1.45	3.46	1.41
Irritability	2.51	1.78	1.68	1.40*
TAS-20				
Total score	54.20	16.16	55.02	12.32
DIF	22.00	6.47	18.06	7.37**
DDF	15.13	6.69	13.98	6.03
EOT	20.18	5.29	20.70	5.94

The sex ratio among patients was similar between the pain and the non-pain groups

MAC Mental Adjustment to Cancer Scale, IBQ Illness Behaviour Questionnaire, TAS-20 Toronto Alexithymia Scale, DIF difficulty in identifying feelings, DDF difficulty in describing feelings, EOT externally oriented thinking

Adapted from Porcelli et al. (2007)

* $p < 0.05$, ** $p < 0.01$

higher scores of “difficulty in identifying feelings” in the *Toronto Alexithymia Scale* (TAS-20) than patients who experienced no pain (Table 2.11).

In general, ill people who also experience chronic pain often also experience various specific emotions, especially fear, anger and sadness, as we have already mentioned (Fernandez and Milburn 1994), and as a result, pain may exact a considerable emotional toll on them (see for example Sela et al. 2002). One important emotional aspect of pain in the context of cancer is the feeling and fear that experiencing pain is an indication that the cancer is progressing (Ahles et al. 1983). Ahles et al. (1983) studied 40 cancer patients, mostly with a metastatic stage of disease, and most of them (61 %) associated pain with fear that the disease was progressing. This in turn brought increased anxiety and hostility–irritability. Although such fear may be biologically justified to some extent, we should stress that it is not always true that pain means disease progression.

Sela et al. (2002) studied 111 advanced cancer outpatients in Canada (53.2 % females), mostly (90 %) presenting evidence of metastasis. The sample included mainly cases of breast, lung, gastrointestinal and genitourinary cancer (76 % of all cases).

Overall, pain was significantly associated with frustration, anger and exhaustion in both males and females. In addition, female patients also showed an association of pain with helplessness/hopelessness. Interestingly, neither sex showed a significant association of pain with fear in this Canadian sample, perhaps suggesting that the association of pain with specific emotions may be variable across ethnic groups and could be modulated by learning and culture.

As we have already seen, cancer-related pain can affect not only behaviours and emotions but also some cognitive functions. So much so that cognitive interventions may be used to reduce pain in cancer patients or to help the patient cope with the effects of pain (see Syrjala et al. 1992; Weisenberg 1998 and references therein). For instance, Weisenberg (1998) lists problem-solving skills, relaxation techniques (such as use of deep breathing and watching pleasant images), cognitive restructuring, self-monitoring, self-reinstruction, use of imagination and self-reinforcement of own effort to change and cope. Albert Bandura terms the conviction that oneself is capable of achieving a specific goal, such as overcoming the distressing effects of pain in this case, *self-efficacy* (Bandura 1977). Self-efficacy can be influenced (increased, for example) through experiences that can be of a purely personal nature or that can also be enhanced by social interactions and training.

As it is applied to therapy, the cognitive approach aims at changing the conception that some patients may have of pain, replacing feelings of hopelessness with those of being in control. In this way it is hoped that the patient may increase his/her threshold of pain tolerance (Weisenberg 1998). This of course may require a specific tailoring of the cognitive intervention to the personal characteristics of the patient, as what works for one patient may not work for another. In addition, Syrjala et al. (1992) have shown that hypnosis can also be an effective intervention to reduce cancer-related pain through alteration of cognitive states.

Hypnosis is achieved through a process of deep relaxation, but other forms of relaxation can also be used to help patients cope with their pain. Syrjala et al. (1995) studied a sample of 94 patients undergoing bone marrow transplant as part of their treatment for a variety of cancers (leukaemia, myelodysplasia or lymphoma). Two treatment groups were used: one comprised individuals who were exposed to relaxation and imagery (e.g. images of a place of the patient's choosing), and the other, the cognitive-behavioural coping skills group, received specific training in various coping strategies and methods of relaxation. Syrjala et al. showed that all groups undergoing cognitive treatment for pain control did in fact reduce their experience of pain. In Chap. 8 we will review several complementary psychological therapies that can be useful in pain control.

All of the above aspects of pain may vary across cultures in their precise modality of expression, and although there may be convergences between groups, divergences may also occur and they should be properly identified and considered in the treatment of patients (McGuire 2004).

Finally, we cannot neglect to mention that although pain may affect the psychology of cancer patients and that some of such effects could be modulated to serve therapeutical purposes, sometimes our thoughts, feelings and beliefs may erect barriers to the management of cancer pain.

Here we describe some of the barriers doctors face or even elevate themselves in the management of pain and/or that patients may also elevate against the prospect of pain management for their cancer condition, including apprehension regarding the use of pain relief drugs. For instance, von Roenn et al. (1993) list “inadequate pain assessment” as being one of the most common barriers against pain management (76 % of respondent doctors mentioning it). Some doctors also indicate “reluctance to prescribe opioids” (61 %) and “inadequate knowledge about pain management” (52 %). Patients, on the other hand, may be reluctant to report pain (62 %) or they may be reluctant to take opioids (62 %).

Cancer patients may not report pain for more than one reason. Ward et al. (1993) list fear of injections, fatalism, concern about the side effects of pain relief medication, fear of becoming addicted to analgesics, desire not to interfere with the actual treatment of the disease by requesting pain relief and concern that pain is an indication of disease progression. In their research, Ward et al. (1993) studied a sample of cancer patients (lymphoma, ovarian, breast, testicular, prostate, colon and others) in the USA and found that the most common barriers for pain treatment were the fear of addiction to pain relief drugs, the fear that pain may indicate progression of the disease and the fear of side effects of the pain management procedures.

Emotions may also become an impediment to the treatment of pain, known as *affective patient-related barriers* (Jacobsen et al. 2009), as can cognitive factors. Among the cognitive barriers, Jacobsen et al. (2009) list fear of addiction to analgesics that we have already mentioned, problems with communication with health caregivers derived from patient’s assumptions about whether it is appropriate or not to express feelings of pain to the doctor or even cultural beliefs about the actual ability of medicine to control pain.

In sum, cancer is often associated with a multifactorial pain experience that involves physiological, sensory, behavioural, affective, cognitive and sociocultural dimensions. Although the pain experience could be modulated by the patient to extract more assistance from his/her social environment than is really required by catastrophising, caregivers should be wary not to push this possibility too far, as neglect of physiological pain that has a direct cancer aetiology may jeopardise treatment and patient’s well-being. On the other hand, patients themselves may erect some barriers to the management of their pain, with fear of addiction to pain-relieving drugs being a frequent barrier.

In the next section we focus on a very common experience associated with cancer: chronic fatigue.

Cancer-Related Fatigue

We normally experience fatigue during our daily activities, and, as such, fatigue is an evolved adaptive response to the expenditure of energy required to sustain bodily functions. Through resting we give our body the chance to repair damaged tissues, damage that is caused by the activity itself or perhaps by an injury or an infection

(Ryan et al. 2007). However, fatigue experienced by cancer patients is somewhat different from the normal daily experience of fatigue: cancer-related fatigue is “disproportionate to exertion level and is not relieved by rest or sleep” (Ryan et al. 2007: 22).

Indeed, if there is one effect of the cancer experience that is common to most individuals it is that of feeling down in energy, tired, weak and slow in the performance of various tasks, in other words, of feeling fatigued. Fatigue may result from the physiological and psychological effects of cancer itself and/or from therapy but also from the stress involved in knowing that one is experiencing a serious illness (Gutstein 2001).

Fatigue is experienced by more than 70 % of cancer patients receiving radiation or chemotherapy (Ancoli-Israel et al. 2001; Schubert et al. 2007); but more generally, between 40 and 96 % of cancer patients experience fatigue (Smets et al. 1993; Richardson 1995; Barnes and Bruera 2002; Ryan et al. 2007; Ray et al. 2008) that can drag on for a variable amount of time after treatment as well, potentially giving shape to a *chronic fatigue syndrome* (Smets et al. 1993; Ray et al. 2008). Some survivors of Hodgkin’s lymphoma may not recover personally acceptable levels of energy even 9 years after treatment. Levels of chronic fatigue experienced by cancer patients are far higher than the prevalence of the syndrome in the general adult population, which varies from 0.006 to 3 % (Afari and Buchwald 2003).

Fatigue tends to be considered a more serious issue by cancer patients than nausea and pain (Schubert et al. 2007). In a study carried out in the UK on patients suffering from various forms of cancer, Stone et al. (2000) found that out of a list of symptoms that included fatigue, alopecia, depression, constipation, pain, dyspnoea (shortness of breath), diarrhoea, nausea/vomiting and weight loss, the symptom that affected the patients most was fatigue, which was mentioned by 58 % of participants. Some of the reasons given to consider fatigue an especially unwelcome effect of cancer and its treatment included decreased ability to enjoy life, including sex life, and also decreased ability to work. In addition, it could be also argued that fatigue may reduce the frequency of engagement in social interactions, which in turn may limit the social support the patient may receive.

Physiologically, cancer-related fatigue has two main components: one that involves a decreased ability of the peripheral neuromuscular tissues to perform the tasks that our brain is set to achieve (*peripheral fatigue*) and a *central fatigue* that is a difficulty of our brain to perform voluntary, self-motivated tasks, even when there are no peripheral neuromuscular impediments to the achievement of such performance (Ryan et al. 2007).

The mechanisms causing central and peripheral fatigue may also interact, producing compounded effects: brain cytokines can affect peripheral fatigue after muscle-damaging exercises (Carmichael et al. 2006). Moreover, as soon as a cancer patient experiences fatigue, he or she may run the risk of being engulfed into a vicious circle whereby decreased levels of activity produced by the initial fatigue lead to lower ability to exert oneself physically, which consequently may increase the sense of tiredness once exercise occurs, thus enhancing the perception of fatigue (Ancoli-Israel et al. 2001). The cycle can be broken by following a program of regular exercise.

A potential biological mechanism that could explain the link between cancer and fatigue is one involving the activity of the immune system. We have already seen how cytokines can influence the activity of the nervous system to affect behaviour, and they are also part of the immune response to cancer. In fact, some studies have found a positive association between experience of fatigue and circulating levels of various interleukins in prostate and lung cancer patients (Bower et al. 2002). Julianne Bower and collaborators carried out a study of 20 “high-fatigue” and 20 “low-fatigue” women who had been diagnosed and treated for breast cancer in the USA. High-fatigue women had higher circulating levels of interleukin-1 receptor antagonist (IL-1ra), sTNF-RII and neopterin (an indicator of immune system activation); they also had lower circulating levels of cortisol, lower percentage of NK cells and macrophages, and they also differed in the ratio of some T lymphocyte types (Landay et al. 1991; Bower et al. 2002). Elevated levels of fatigue are also experienced by patients who have higher levels of circulating TNF- α and transforming growth factor- β (TGF- β) (Gutstein 2001).

Even more direct evidence for cytokines mediating the expression of fatigue in cancer patients comes from cases where interferon is used in treatment. In such circumstances fatigue is “the most prevalent symptom, the most important dose-limiting toxic effect, and the most difficult side-effect to manage” (Richardson 1995: 23). Alison Richardson reports the results of works by Quesada et al. (1986) and Piper et al. (1989) indicating that cancer patients undergoing immunotherapy that used interferon, interleukins (IL-6, IL-12, IL-1 β , IL-2), tumour necrosis factor and colony-stimulating factors experienced significant levels of fatigue, sometimes to the extent that therapy had to be interrupted (Richardson 1995, see also Schubert et al. 2007).

In a recent meta-analysis of 18 published studies, Christian Schubert and collaborators showed that there is a significant positive correlation between levels of pooled circulating inflammatory markers and fatigue. When individual inflammatory markers (including cytokines) were analysed, they found that IL-6, IL-1ra and neopterin (a pteridine) were all positively correlated with fatigue. Correlations were not statistically significant for IL-1 β and TNF- α (Schubert et al. 2007).

It is widely reported that chemotherapy and radiotherapy themselves may cause fatigue. Again, evidence suggests that such effect may be modulated by cytokines. For instance, drugs such as tamoxifen, cisplatin and paclitaxel that are used in chemotherapy increase circulating levels of some cytokines (Ray et al. 2008).

We have already seen in this chapter how cancer-induced production of cytokines can be associated with decreased serotonin production. Serotonin dysregulation has been linked to the onset of central fatigue (Afari and Buchwald 2003; Ryan et al. 2007). Cytokines, of course, also affect fatigue in perfectly healthy persons, not just cancer patients (Afari and Buchwald 2003; Lorusso et al. 2009).

From the perspective of behaviour, specific correlates of fatigue in cancer patients include somnolence, decreased activity level, forgetfulness, decreased interest in social activities, depressed mood, anxiety, getting easily distracted, sleep disturbance and decreased cognitive abilities (Wessely 2001; Bower et al. 2002; Afari and Buchwald 2003; Reuter and Härter 2004; Ray et al. 2008). Fatigue makes the patient feel vulnerable, fearful and also angry and frustrated at not being able to perform

what previously were trivial tasks (Richardson 1995). Such behavioural correlates of cancer-related fatigue do not necessarily occur in all individuals, or with the same intensity across the various cases, there is indeed great variability that is caused by both personal and environmental factors.

With the emphasis put in modern society on alertness of mind, speed and efficiency of mental processing at work and in social interactions in general, it is no wonder that the disruption of cognitive abilities caused by cancer-related fatigue can be perceived as a serious problem by patients, with over 85 % of patients complaining about some deficiency in cognitive performance (Afari and Buchwald 2003). Interestingly, such high level of concern does not need to be reflected in a significant decrease in mental faculties as measured through more objective tests; a personal dissatisfaction based on self-perception of performance in a competitive social environment will almost inevitably magnify the effects of any measurable change in cognitive faculties. In addition, through its effects on mood and level of activity, fatigue may negatively impact upon social interactions and, ultimately, quality of life (Valentine and Meyers 2001; Bower et al. 2002).

Fatigue tends to be positively correlated with depression, and Visser and Smets (1998) suggest that at least some aspects of general and physical fatigue seem to actually cause a depressive mood. This association between fatigue and depression is also supported by the use of psychological coping strategies to control fears in cancer patients; the enactment of such coping strategies seems to improve both fatigue and depression (Ray et al. 2008). Understandably, fatigue may also be a more straightforward side effect of lack of rest and sleeplessness caused by cancer, cancer therapy or both (Ancoli-Israel et al. 2001, see next section).

In sum, fatigue is one of the most common and also most frustrating effects of cancer and its treatment as reported by patients. It can affect normal daily activities through modifying mental performance and social interactions. By altering the level of activity and also cognitive faculties and mood states such as depression, fatigue can seriously affect the quality of life. The expression of cancer-related fatigue is plausibly mediated by the activity of cytokines.

In the next section we focus on the disruption of sleep patterns suffered by cancer patients.

Sleep Disorders and Cancer

Sleeping is a normal behaviour that usually manifests itself in daily (circadian) patterns comprising an initial deep sleep phase that is characterised by non-rapid-eye-movement (NREM) followed by a rapid-eye-movement (REM) sleep phase. We typically experience dreams during the REM phase. NREM and REM phases occur in cycles during sleep of about 90-min duration that repeat themselves several times (Lee et al. 2004a; O'Donnell 2004). Individuals differ in their specific modalities of sleeping, with the best sleeps being those that are in tune with our own personal needs (Lee et al. 2004a). When the normal patterns of sleep are disturbed, we may experience *insomnia* (sleeping much less than expected in healthy individuals) or

hypersomnia (sleeping more, including during daytime or outside the usual hours of sleep) (Ancoli-Israel et al. 2001).

Sleep disorders in general, and sleeping patterns of cancer patients in particular, can be studied through the use of *polysomnography* which involves the monitoring of various relevant body functions during sleep, such as brain activity, heart rhythm, breathing activity, eye movement, muscle activation and degree of blood oxygenation. Polysomnography affords the medical practitioner the opportunity to characterise the sleeping patterns of the patient in a more objective manner. Studies of sleep disorders have been carried out in cancer patients using polysomnography showing that cancer therapy such as chemotherapy may be associated with light sleep and less REM sleep (Fiorentino and Ancoli-Israel 2006). An important issue with polysomnography, however, is that it only contributes a physiological snapshot of sleeping. Additional information is required from the patient through interviews or responses to questionnaires to provide a more comprehensive picture of the personal situation of the patient in terms of the behavioural, emotional and cognitive aspects of insomnia.

Although insomnia may be experienced by otherwise perfectly healthy individuals, in which case it is known as *primary insomnia*, when it is a side effect of a concomitant condition such as cancer, it is denominated *co-morbid insomnia*. Insomnia may also affect the individual at different stages of the process of sleeping. Difficulty in falling asleep, or sleep latency, characterises *initial* or *sleep-onset insomnia* (Fiorentino and Ancoli-Israel 2006), which is experienced by about 44 % of cancer patients with sleep disorders (Simeit et al. 2004). If the individual has problems maintaining sleep, then he or she is experiencing *middle* or *sleep maintenance insomnia* (about 76–90 % of patients, Simeit et al. 2004). On the other hand people who wake up too early in the morning may be experiencing *terminal* or *late insomnia* (84–85 % of patients, Simeit et al. 2004). A variable 35–75 % of cancer patients may have problems getting back to sleep once awoken at night, and about 37 % have problems with being sleepy during daytime (Simeit et al. 2004). Finally, although an individual may be able to achieve some degree of sleep at night, such sleep may be *non-restorative*, that is, the individual wakes up still tired. These problems may occur alone or in various combinations. Such conditions may be chronic, if lasting for more than 4 months; short term if lasting for 2–4 weeks or transient if lasting for less than 2 weeks (Graci 2005; Fiorentino and Ancoli-Israel 2006; Davidson et al. 2007). However, transient conditions may recur.

Arthur Spielman (1986, see also Graci 2005) proposed a three-factor model of insomnia in which he identified:

- *Predisposing conditions*: such as being female, degree of arousability, having older age, decreased sleep drive and personal and also family history of mood and anxiety disorders
- *Precipitating factors*: such as stress, cancer, pain, immunological and thermoregulatory changes, cancer therapies, menopausal symptoms and various environmental factors.
- *Perpetuating factors*: such as poor sleep routine (daytime napping, spending too much time in bed), conditioning, depression and anxiety, false expectations, inappropriate use of medication and false perception of own condition.

It is estimated that about 6–33 % of the general adult population suffers from some form of insomnia (Spielman 1986; Graci 2005; Fiorentino and Ancoli-Israel 2006; Roth 2007). Sleep disturbance is also routinely reported in patients suffering from various forms of cancer from breast, colon, lung, melanoma and lymphoma to prostate, gynaecological and head and neck (Lee et al. 2004a). Studies of sleep patterns among cancer patients have described a range of between 19 and 95 % of patients experiencing some form of sleep difficulty (Fortner et al. 2002; Fiorentino and Ancoli-Israel 2006; Davidson et al. 2007). For cancer patients undergoing radiotherapy, Beszterczey and Lipowski (1977) found that 45 % of them slept for an average of less than 50 h/week, with 23 % sleeping less than 40 h on average. The authors identify depression as the most important factor affecting the capacity to sleep. It seems therefore that on average cancer patients are more likely to suffer from disturbance of their sleeping patterns than members of the general population (see also Savard et al. 2001). In particular, breast cancer patients are especially prone to be affected by sleep problems (Savard et al. 2005a). In addition, it is often the case that insomnia experienced by many cancer patients tends to persist over a variable number of years beyond the end of treatment (*chronic insomnia*) (Savard et al. 2001; Graci 2005).

Fortner et al. (2002) carried out a study of insomnia in 72 breast cancer patients in the USA. Although they did not find a statistically significant difference in sleeping patterns between these patients and a control sample of non-cancer patients, breast cancer patients did take significantly more sleep medications than controls, suggesting that they did have issues with their sleeping after all. Mercadante et al. (2004) studied 123 patients suffering mainly from breast, lung, colon, prostate or rectum-sigma cancer. Among those patients, insomnia was associated with anxiety, fatigue, drowsiness and nightmares. Sleeping difficulties were also described by Savard et al. (2001) in a Canadian study of 145 female patients who received non-metastatic breast cancer treatment: they reported that 48 % of patients had problems with sleeping. The patients associated such difficulties mainly with the worries and stress consequent to cancer, with cancer treatment magnifying such an effect. Indeed insomnia usually occurs as part of a complex of psychological symptoms that also include fatigue, pain, depression and anxiety (Theobald 2004).

In a recent study carried out in the USA on 33 breast cancer patients and 23 prostate cancer patients, Thomas et al. (2010) found that sleep patterns gradually improved with time in those patients, mainly due to the adoption of avoidance coping strategies to tackle depression, whereas the same patients took longer to fall asleep when they were depressed. *Avoidance coping* involves responding to a source of stress by ignoring it, repressing it or diverting one's attention away from it. This is contrasted by *approach coping* which implies a more active involvement of the individual into seeking information about the stressor and monitoring its effects (see for example Bernard et al. 2004, see also Chap. 5). Interestingly, male patients suffering from prostate cancer who also displayed approach coping showed a decrease in sleep latency (i.e. they improved their sleeping patterns) over time.

This suggests that specific coping strategies may aid in improving cancer-associated sleeping problems in a patient-specific manner.

Parker et al. (2008) carried out a polysomnography study of the sleep/wake patterns of 58 male and 56 female advanced cancer patients in the USA. What the authors found was that participants had difficulties maintaining any state, whether sleep or wake. This was associated with an almost absent slow-wave sleep stage, a stage that is indicative of the need to sleep. They also recorded REM during daytime, an unusual occurrence in healthy individuals that is associated with sleep deprivation and sleep disorders.

Cancer and its treatment may affect insomnia in many ways, through various psychological and also physical mechanisms (see Fig. 2.7). Conversely, chronic insomnia can also produce both physiological and psychological effects. Among the potential physiological effects of insomnia are asthma, gastroesophageal reflux disease, irritable bowel syndrome, fibromyalgia (pain of muscular and connective tissue origin) and decreased immunocompetence. Psychological effects include problems of concentration, mood changes, problems with memory, tiredness, increased anxiety and also depression, loss of capacity to experience pleasure and decreased quality of life in general (Graci 2005; Fiorentino and Ancoli-Israel 2006; Davidson et al. 2007). As we have already seen for the case of fatigue in the previous section, psychological effects of insomnia may also exert an escalating (positive-feedback) effect whereas specific states of mind caused by insomnia such as depression may in turn increase the level of sleeplessness, thus leading to even more stress, depression and then further insomnia (Roth 2007).

Cancer-related insomnia may also compromise some cognitive abilities. Taylor et al. (2003) for instance studied 18 cancer patients who suffered from acute insomnia and 15 cancer patients experiencing persistent insomnia (males and females were included in both samples). The most common forms of cancer suffered by these patients affected breast, lung, thyroid, larynx, ovaries, immune system (Hodgkin's lymphoma) and testicles. Both groups of patients showed an attentional bias for words related to cancer, but attentional bias for words related to sleep was shown only by patients in the persistent insomnia group. Such attentional bias could potentially reinforce the distress that may cause insomnia in the first place, but on the other hand it may perhaps be used to support cognitive therapies to treat insomnia. This close relationship between cancer, sleep, behaviour and cognition can proceed in a bidirectional way as shown in Fig. 2.7, which suggests that cognitive and behavioural therapies could be devised to ameliorate the sleeping patterns of cancer patients.

In fact, cognitive-behavioural therapies (CBT) are being currently developed to treat insomnia in cancer patients. CBT use a three-pronged approach to address sleep problems: (a) there is a *cognitive* aspect that aims at restructuring thoughts and ideas that may interfere with resuming a more normal pattern of sleep; (b) there is a *behavioural* aspect such as controlling the stimuli that may interfere with sleep and establish sleep routines and (c) there is an *educational* aspect that aims at redirecting the sleeping preferences of the patient to more appropriate modalities (Fiorentino and Ancoli-Israel 2006). According to Fiorentino and Ancoli-Israel (2006), such

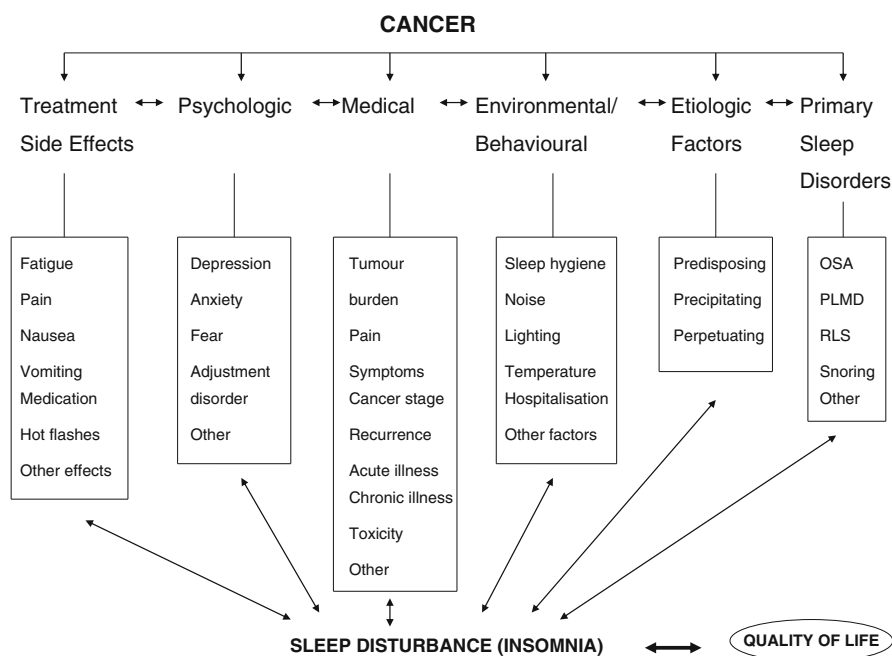


Fig. 2.7 Mechanisms by which cancer may affect insomnia, with cascading consequences on the quality of life of patients. *OSA* obstructive sleep apnoea, *PLMD* periodic limb movement disorder, *RLS* restless leg syndrome (adapted from Graci 2005)

CBT aims at controlling the perpetuating factors of insomnia such as maladaptive thoughts and behaviours. Graci (2005) identifies five major categories of CBT that are currently being employed to address the issue of insomnia in cancer patients:

- *Sleep hygiene*: The patient is guided towards the performance of activities that minimise disruption of sleep, such as reducing consumption of drugs, increasing exercise and keeping regular schedules of activities during the day.
- *Stimulus control*: Teaching schedule that aims at conditioning the patient to associate bed and sleeping and to establish a regular sleeping routine.
- *Sleep restriction*: Gradual step-by-step achievement of longer sleeping hours by consolidating any initial shorter sleeping hours to then gradually increase the time until a more acceptable sleeping time is achieved. In this process the patient is directed to only spend sleeping time in bed, until all time in bed is spent sleeping for a sufficient number of hours.
- *Progressive muscle relaxation*: The patient is taught to relax and stretch a progressive number of body sections until the full body feels relaxed.
- *Guided imagery*: The patient is invited to adopt a comfortable position and to feel relaxed, satisfied and without pain whilst also listening to an appropriate sound recording by which relaxing effects are enhanced by a specifically trained health practitioner.

Josée Savard and collaborators (Savard et al. 2005a) have evaluated the effectiveness of CBT in reducing insomnia in 57 female breast cancer patients. Their treatment involved group sessions that combined various aspects of CBT including stimulus control, sleep restriction and sleep hygiene among others. Results indicate that CBT had the effect of improving the patterns of sleep, decreasing anxiety and depression and achieving an overall betterment of the patient's quality of life. On the other hand, Simeit et al. (2004) improved various sleep parameters in cancer patients through the use of relaxation techniques. Therefore applications of CBT in the treatment of sleep disorders are certainly producing encouraging results. We will return to this issue in section "[Cognitive Therapies](#)" of Chap. 8.

Insomnia is also associated with an elevated activation of the hypothalamo-pituitary-adrenal axis which is responsible for the observed relationship of insomnia with elevated levels of adrenocorticotrophic hormone, cortisol and catecholamines in circulation (Roth 2007). We have already seen in this chapter how corticosteroids can be associated with production of cytokines and how cytokines can be involved in the mediation of behaviours that characterise the sickness syndrome in cancer patients. Cytokines have also been involved in the regulation of the sleep/wake cycle (O'Donnell 2004). In particular, circulating levels of IL-6 and TNF- α peak during sleep, and cytokines such as interferon, that are used in cancer immunotherapy, can also affect sleep patterns (Moldofsky and Dickstein 1999; O'Donnell 2004).

In general, substantial sleep deprivation is associated with activation of the immune system, whereas partial sleep deprivation is associated with lowered immune activity (Savard et al. 2005b). Such immune downregulation is observed in NK cells and some lymphocytes. Savard et al. (2005b) carried out a study assessing the effect of CBT to control insomnia on the activity of various components of the immune system. They studied 57 women who had received breast cancer treatment. The subjects were suffering from chronic insomnia that followed cancer diagnosis. Patients undergoing CBT had higher levels of IFN- γ and IL-1 β and lower number of lymphocytes compared with controls.

That is, yet again it seems that the molecular bridge between cancer and behaviour (sleep disorders in this case) may be provided by the cytokines, and, through the cytokines, behaviours such as those that could limit insomnia may be used to improve the patient's immune capabilities in the fight against cancer.

In sum, it is often the case that cancer patients suffer from altered patterns of sleeping. Insomnia in particular is a very common condition associated with various forms of cancer. CBT have been recently developed to deal with insomnia in cancer patients, and their use may help the patient to gradually readjust his/her sleeping routine. Cytokines seem to provide a molecular link between cancer and sleeping behaviour.

The sleep/wake cycle that was the subject of this section is a specific biological rhythm that is circadian, meaning that it usually repeats itself approximately every 20–30 h. In the next section we analyse the association between cancer and disruption of circadian rhythms more generally.

Circadian Rhythms and Cancer

We have seen how cancer may disrupt the circadian sleep/wake cycle with consequences for behaviour. Many aspects of our biology show rhythmic daily fluctuations; these include temperature, evoked brain potentials, production of corticosteroids, catecholamines, melatonin, human growth hormone and thyroid-stimulating hormone, release of electrolytes via the urine, intestinal peristalsis, heart rate, blood pressure, liver and renal plasma flows, immune activity and secretion of digestive enzymes into the gastrointestinal tract (Kerkhof 1985; Fu and Lee 2003; Levi and Schibler 2007; Spiegel 2008). Some aspects of personality such as extraversion/introversion may also fluctuate within the day.

Circadian rhythms have an adaptive value in organising the activities of the organism so that survival and lifetime reproductive success are maximised in the face of predictably and periodically changing environmental circumstances (Fu and Lee 2003). Depending on the period of the cycle, biological rhythms may be broadly classified as *infradian* (period shorter than 20 h), *circadian* (period between 20 and 30 h) and *ultradian* (period longer than 30 h) (Levi and Schibler 2007).

Circadian rhythms in mammals are controlled by the brain suprachiasmatic nucleus (SCN), an area of the hypothalamus. The SCN is regarded as the “master pacemaker” or “clock” of circadian rhythms (Chen-Goodspeed and Lee 2007) being composed of many single-cell oscillators that produce coordinated circadian patterns of activity when they operate in synchrony (Fu and Lee 2003). The clock responds to regular patterns of change in the external environment, being more active during the day and less active at night-time. The sleep/wake circadian clock for instance is maintained by environmental light activating eye photoreceptors that subsequently stimulate the SCN via the retinal-hypothalamic tract.

The SCN mainly projects to the rest of the hypothalamus but to a lesser extent also to the thalamus and basal forebrain (see Fig. 2.8), with the latter two, in turn, projecting to the neocortex, hippocampus, various structures of the limbic system and basal ganglia. It is through these neuronal connections between the SCN and other parts of the brain that circadian rhythms affect mental faculties such as attention, memory and emotions.

Rhythms are also controlled internally by specific genes, the so-called clock genes. Clock genes control aspects of the cell cycle, programmed cell death (apoptosis) and cell reproduction that can affect circadian cycles when those genes are expressed in the appropriate tissues (Ray et al. 2008). So far, eight genes have been identified that affect circadian rhythms: *clock*; *casein kinase 1 ϵ* ; *Period1*, *Period2* and *Period3*; *Bmal1* and *cryptochrome 1* and *cryptochrome 2* (Fu and Lee 2003).

Circadian rhythms tend to become disrupted with age, whereas sex differences seem to be inconsistent across studies (Kerkhof 1985). Cancer development is also associated with disruption of circadian rhythms, and vice versa disruption of circadian rhythms may affect the onset and progression of cancer. This two-way causal link between circadian rhythms and cancer was already suggested by the early works

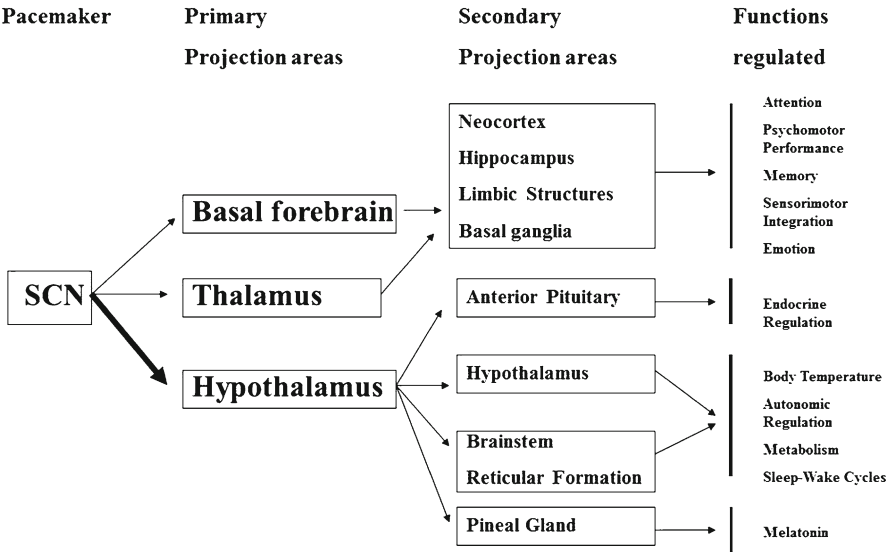
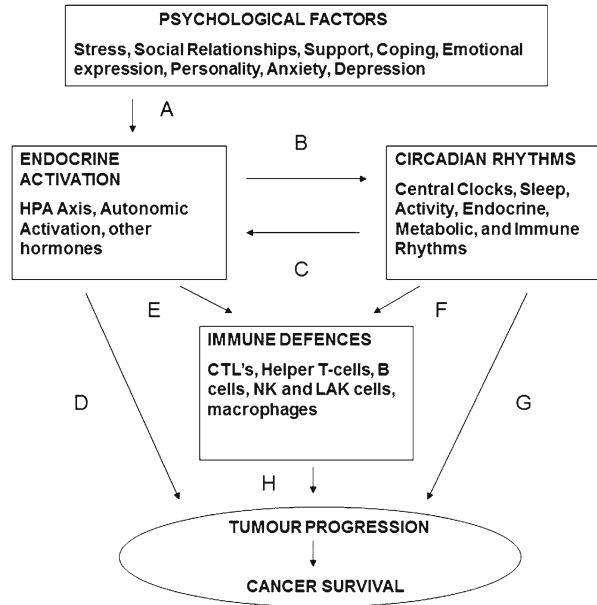


Fig. 2.8 Neuronal projections of the hypothalamic suprachiasmatic nucleus (SCN) pacemaker and the functions it controls. Note that the most intense primary projection of the SCN is to other areas of the hypothalamus (adapted from Moore 1997)

on breast tumours carried out by Wolfgang Jöchle and T. Hamilton in the 1960s (Jochle 1964; Hamilton 1969). Shift workers for instance have been documented to suffer from cancer (breast for women, prostate for men) at especially high frequencies; the same for long-haul flight attendants (Reynolds et al. 2002; Filipski et al. 2006; Schernhammer et al. 2006; Chen-Goodspeed and Lee 2007; but see Pukkala et al. 2002; Kojo et al. 2005 for non-supportive evidence regarding cancer risk in flight attendants). Filipski et al. (2006) carried out an experiment in mice to determine the effect of alteration of circadian rhythms on cancer development. The disruption of circadian rhythms in their experimental animals was achieved by either ablating the SCN through a bilateral electrolytic lesion or subjecting them to a “jet-lag”-equivalent regime of disruption of the light–dark daily phases. The mice were subsequently transplanted a 4 × 4-mm tissue sample of either Glasgow osteosarcoma or pancreatic adenocarcinoma to determine the effect of circadian rhythm disruption on tumour growth. Both tumours grew faster in mice suffering the SCN lesion than in control mice, and Glasgow osteosarcoma also grew faster in “jet-lagged” mice.

Conversely, cancer itself may cause dysregulation of various biological rhythms. For instance, patients suffering from stomach, breast, prostate, ovarian and colon cancer have altered circadian cycles of melatonin, prolactin, cortisol, luteinising hormone, gonadotropin hormone, thyroid-stimulating hormone, follicle-stimulating hormone and also altered temperature regulation and lymphocyte and various peptide production as a result of their cancer (Sephton and Spiegel 2003).

Fig. 2.9 Various mechanisms may explain the effect of psychosocial factors such as stress and others (A) on cancer onset and progression (D, G, H). These include mutual endocrine-mediated alteration of circadian rhythms (B, C), such as those affecting release of cortisol in circulation, leading to changes in the levels of immune defence (E, F). CTL cytotoxic T lymphocytes, NK natural killer cells, LAK lymphokine-activated killer cells. Redrawn from Sephton and Spiegel (2003)

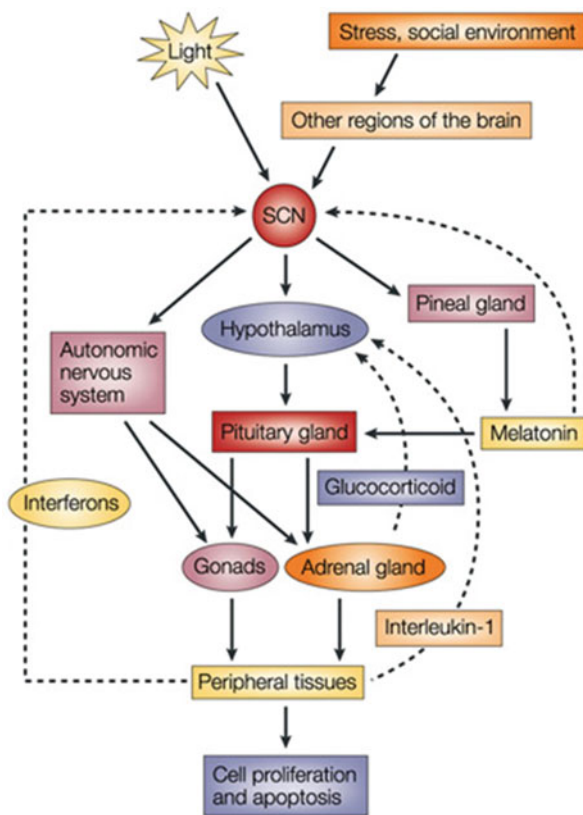


Chemotherapy can also disrupt circadian rhythms, and such disruption has been associated with a decrease in survival rate in metastatic colorectal cancer patients (Innominato et al. 2012).

One especially important circadian rhythm associated with cancer is that of cortisol. Healthy individuals show circadian rhythms of cortisol levels in circulation, with the peak in concentration being observed in the early morning, from 5 to 9 am, to gradually decrease as the day unfolds (Morrow et al. 2002). Cortisol is one of the hormones that mediate the stress response; therefore, altered patterns of daily cortisol fluctuations in cancer patients may be evidence of dysregulation of the stress response. Stresses that can cause corticosteroid dysregulation in cancer patients may be directly caused by the cancer itself or they could be consequences of psychological factors. Moreover, altered glucocorticoid levels have been associated with diminished abilities of patients to fight tumours (Spiegel 2008). In a study of 104 female patients with metastatic breast carcinoma, Sephton et al. (2000) demonstrated that survival was decreased in patients that did not show strong diurnal fluctuations in cortisol; such patients also had lower levels of circulating NK cells, suggesting that low cortisol may decrease the level of trafficking of NK cells within the body, thus lowering the efficiency of immune attack against cancer. Whenever psychological stresses, such as those resulting from the loss of a partner, become chronic, then cortisol levels may lose their habitual circadian rhythm, with potential consequences for cancer development (see Fig. 2.9 and Sephton and Spiegel 2003).

Another important hormone that links circadian rhythms with cancer is melatonin. The pineal gland mainly but also the retina and cells of the immune system produce

Fig. 2.10 Neuro-immuno-endocrinological mechanisms by which circadian rhythms controlled by the suprachiasmatic nucleus (SCN) may affect cancer onset and progression via modulation of cell proliferation and programmed cell death (apoptosis) (from Fu and Lee 2003)



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melatonin, a molecule that can act as a modulator of the activity of the immune and nervous systems. In addition, melatonin has also a pivotal role in the maintenance of the light–dark cycle, with circulating levels fluctuating according to a circadian rhythm: high at night and low during the day (Miller et al. 2006) that also directly affect the activity of the SCN (Moore 1997). Melatonin has a very important immuno-enhancing role that is mediated by cytokines (see Miller et al. 2006 for a detailed review). Another action of melatonin is that of suppressing the production of oestrogens by the ovaries; this means that when women are regularly exposed to light at night-time, because of night shift work for instance, they experience depressed levels of melatonin and consequently higher than normal levels of oestrogens, thus increasing their risk of developing breast cancer in an age-dependent manner (Sephton and Spiegel 2003).

To recap, Fig. 2.10 summarises the major neuro-immuno-endocrinological mechanisms that allow circadian rhythms controlled by the SCN to affect cancer onset and progression via the modulation of cell proliferation and programmed cell death (apoptosis). Both changes in light/darkness cycles—such as those associated

with specific jobs—and various kinds of stresses, including social stresses, may alter the activity of the SCN that in turn affects the usual operation of various parts of the nervous system, including the hypothalamus and the pineal gland in the brain. These in turn modify the production of melatonin and steroid hormones that can finally affect the activity of the immune system, thus altering the body's ability to defend itself against tumours.

In the next section we focus on another common experience of many cancer patients that can significantly affect behaviour and the performance of daily activities: nausea.

Cancer and Nausea

Nausea is not an uncommon experience for cancer patients, being often associated with vomiting (*emesis*, as it is also referred to in the medical literature). Both nausea and vomiting are especially common in advanced cancer patients, affecting between 30 and 67 % of patients (Reuben and Mor 1986; Davis and Walsh 2000), especially those with leukaemia, pancreatic, stomach and breast cancer (Reuben and Mor 1986). *Retching* is a “spasmodic movement of the diaphragm and abdominal musculature” (Davis and Walsh 2000: 444) that may or may not co-occur with nausea and vomiting. These conditions can seriously affect the quality of life of patients and in the most extreme of cases worsen the medical situation. Some of the consequences of persistent vomiting may include malnutrition, electrolyte changes, oesophageal damage, depression, helplessness, reluctance of the patient to continue with cancer treatment and, in general, decreased quality of life (Ballatori and Roila 2003; Watson and Marvell 1992). Nausea can be a result of cancer itself (Chang 1981) or, more often than not, of cancer treatment (Watson et al. 1998; Morrow et al. 2002; Warr 2008).

Nausea may follow from cancer through the metabolic effects of the disease (such as hypercalcaemia) or through it causing alterations of the gastrointestinal function or central nervous system activity (Warr 2008). Cancer may also cause alterations of the activity of the autonomic nervous system, thus producing nausea (Bruera et al. 1987). Such autonomic link is evidenced by the association of nausea with pupil dilatation, salivation, cold sweats, tachycardia, pallor and diarrhoea (Davis and Walsh 2000; Morrow et al. 2002) that are under autonomic control. There is a trend for low levels of cortisol to be associated with increased nausea and vomit, although the specific mechanism involved in this link is still unclear (Morrow et al. 2002).

There is also an association between nausea and more complex behaviours via various central nervous system links. For instance, a cognitive effect on the onset of nausea is suggested by cases where cancer patients are unaware of their disease state (as in the case of patients with a mental retardation), patients are not told about potential side effects of therapy or patients have a more positive attitude about their

condition; in such cases nausea may be uncommon during and also after chemotherapy (Chang 1981). Conversely, cognition may enhance the effects of cancer on nausea as in the case of patients who reluctantly undergo chemotherapy (Chang 1981). Apart from cognition, emotions such as anxiety, frustration and anger may also be associated with nausea and vomiting (Chang 1981; Davis and Walsh 2000).

Nausea, vomiting and retching are often expressed in cancer patients as a direct result of therapy. Cancer drugs vary greatly in their effects on nausea, affecting a variable percentage of patients from <10 to >90 % (see Morrow et al. 2002). Some such effects also vary according to age and sex of the patient. Younger patients tend to experience more nausea than elderly patients, and female patients suffer more from nausea than males during chemotherapy (Morrow et al. 2002). Some personality traits may also be linked to nausea during chemotherapy. For instance, *absorption*, or ability to concentrate in the performance of specific tasks, is a personality trait that has been associated with sensitivity to stressful situations and also development of chemotherapy-induced nausea and fatigue (Zachariae et al. 2007). Zachariae et al. (2007) studied 125 female breast cancer patients who were receiving chemotherapy at the Aarhus University Hospital in Denmark. A total of 92.6 % of patients reported experiencing post-treatment nausea, especially after the sixth session of chemotherapy; such nausea was positively associated with absorption.

The age and sex variability in the experience of cancer-associated nausea mentioned in the preceding paragraph may be in part explained by the action of learning and cognitive mechanisms. Through learning, patients may also express *anticipatory nausea* which may develop through classical conditioning, as it usually manifests itself after a few courses of chemotherapy (Morrow et al. 1991). In anticipatory nausea, patients associate an initial experience of nausea during chemotherapy with specific aspects of the medical setting for instance, which become the conditioned stimulus that will elicit nausea on the next occasion the patient comes to the clinic, before any drug is administered. Classical conditioning, however, may not be the only psychological mechanism at the root of anticipatory nausea. Social learning may also have an effect, especially in cases where the patient receives chemotherapy in a room where other patients are doing the same, with some of them perhaps showing evident distress (Watson and Marvell 1992). In addition, cognition and emotions may also be involved in the experience of nausea during chemotherapy even for patients who undertake chemotherapy for the first time (Watson and Marvell 1992), as when the patient may already have expectations that the therapy causes nausea, which may predispose him or her to actually experience it. That is, patients having specific ideas (schemata) that bias their expectations and perceptual experience could be especially inclined to experience nausea. Those patients not holding such expectations may be less likely to experience nausea (see Morrow et al. 2002 for empirical examples). Anticipatory nausea is thought to develop in about 14–42 % of cancer patients undergoing chemotherapy (Watson and Marvell 1992; Morrow et al. 2002; Aapro et al. 2005), whereas anticipatory vomiting is thought to develop in 4–19 % of cancer patients (see Watson and Marvell 1992 and references therein).

Aapro et al. (2005: 118, see also Morrow et al. 1991) list the following risk factors for the development of anticipatory nausea which we report here verbatim:

1. Age <50 years
2. Nausea and vomiting after the last chemotherapy
3. Describing nausea after the last treatment as “moderate, severe or intolerable”
4. Reporting the side effect after the last treatment “warm or hot all over”
5. Susceptibility to motion sickness
6. Experiencing “sweating” after the last treatment
7. Experiencing “generalised weakness” after the last treatment
8. Increase in family conflict
9. Personality factors

Maggie Watson and Catherine Marvell (1992: 98) provide a rather dramatic anecdotal example of anticipatory nausea/vomiting in the case of a patient “who reported vomiting in the hospital shop when she saw a member of staff who had previously been involved in giving her treatment”. In fact some experiences of nausea may not involve the perception of an actual stimulus at all, as even the thought of chemotherapy may trigger nausea in some patients (see Watson and Marvell 1992; Watson et al. 1998 for reviews).

Watson et al. (1998) carried out a study of 100 breast cancer patients receiving chemotherapy. Of those patients, 43 reported experiencing anticipatory nausea during their chemotherapy treatment, but 76 reported post-infusional nausea. Anticipatory vomiting was only reported by 6 patients, whereas 39 patients reported vomiting after receiving treatment.

Finally, anticipatory nausea may also be affected by personality traits of the patient, with Watson and colleagues (Watson and Marvell 1992; Watson et al. 1998) mentioning an association of anticipatory nausea with an inhibited personality style and also living in a chronic state of tension.

In sum, it is not uncommon for cancer patients to experience nausea, which is sometimes associated with vomiting and/or retching. Nausea may be caused by cancer itself and/or by cancer treatment. From a psychological perspective, nausea may affect and is being affected by cognitive, emotional and personality characteristics of the patient.

In the last section of this chapter we review the relationships between cancer and changes in sensory perceptions.

Cancer and the Senses

Whenever cancer affects sensory capabilities, its impact on the life of both patients and family may be significant. Sensory losses may alter food intake with cascading effects on health (malnutrition) and psychology (depression). Decreased visual acuity affects mobility and the performance of many basic daily tasks; hearing loss affects the ability to communicate appropriately, thus potentially leading to social

isolation (Schiffman 2007). The senses may also be affected indirectly by cancer, through side effects of the primary tumour on other tissues; these are the so-called *paraneoplasias* (Thirkill 1994). For instance, some paraneoplasias may be produced by an autoimmune reaction that develops in the organism as a result of cancer (Peterson et al. 1994). In the following five subsections we review our current knowledge of how cancer affects the performance of the senses and how such altered performance may compromise the ability of the patient to function in life. We start with the analysis of the effects of cancer on vision to continue with hearing, touch, temperature sensitivity, olfaction and finally taste.

Vision

Vision can be directly affected by cancer as in the case of retinoblastoma (Chintagumpala et al. 2007) or more often than not it can be affected indirectly, as when the cancer is primarily developing in areas of the body outside the visual organs. In the latter case, altered vision becomes a side effect of cancer or *paraneoplasia*. A common paraneoplasia is associated with cancer-induced autoimmunity that results in damage to the retina (*autoimmune paraneoplastic retinopathy*), leading to impaired vision (Thirkill 1994; Grazyna et al. 1997). This phenomenon was first described by Sawyer et al. in 1976 after studying three patients diagnosed with small-cell carcinoma of the lung. The specific involvement of autoimmunity was subsequently demonstrated by Kornguth and collaborators in 1982. In this case cancer elicits a hyperactive response from the immune system that can turn against healthy tissues of the body, such as the retina. Another paraneoplasia affecting visual acuity is *paraneoplastic optic neuritis* (PON), which may also result from autoimmune processes. PON may occur as a side effect of cancers such as lymphoma, leukaemia and carcinoma, and it may affect central nervous system tissues, including the cerebellum, potentially leading to both dementia and visual impairment (Thirkill 1994). Retinopathy has also been described in association with melanoma. Therefore directly or indirectly, cancer may affect vision, a causal link that is not all that surprising. Less intuitively, however, altered vision may in turn affect the onset of cancer (see, for example, Verkasalo et al. 1999).

As we mentioned in “[Circadian Rhythms and Cancer](#)” section, melatonin is a polypeptide hormone produced by the pineal gland in the brain, whose main function is to couple various biological functions into circadian rhythms. In people with unaltered sense of vision, melatonin reaches its highest levels early in the morning to then decline during the day. We have already seen that melatonin can protect against cancer through its immuno-enhancing properties. In people who are seriously blind, and who therefore do not directly differentiate between day and night, levels of melatonin may be maintained high throughout the 24-h cycle, thus affording greater protection against some forms of cancer. In fact, there are reports of fewer cases of breast cancer among blind women (see Verkasalo et al. 1999 and references therein). Pia K. Verkasalo and collaborators carried out a study in Finland

to determine the association between various degrees of blindness and breast cancer. What they found was that the relative incidence of breast cancer decreased continuously with increased degree of visual impairment in women.

On the other hand, visual impairment may also result from cancer treatment. Chemotherapy for instance may produce effects on vision that range from impaired adaptation to night vision to severe loss of visual capability leading to blindness (Schiffman 2007).

Hearing

As for the case of vision, cancer may also affect hearing through direct effects on the auditory system or indirectly via cancer treatment (radio- and chemotherapy). Both carcinoma and melanoma can develop in the external ear (Byers et al. 1980; Lewis 1987; Stockley and Stucker 1987), whereas the middle ear can be affected by various forms of cancer (Morton et al. 1984) that may result in impaired hearing.

Effects of cancer therapy on hearing are variable. Strumberg et al. (2002) studied 30 long-term survivors of testicular cancer, 63 % of which did not experience any hearing problems. The others suffered from a variety of hearing impairments ranging from unilateral to bilateral hearing reduction of between 5 and 45 %, although results were confused by previous medical conditions such as diabetes mellitus, otitis media and also noise exposure. In a review article, Raaijmakers and Engelen (2002) have indicated the paucity of data regarding the effects of radiotherapy on hearing. They concluded that about a third of patients may develop some degree of hearing impairment depending on radiation dose, when such radiation is applied to regions near the inner ear. Head and neck cancer patients in particular, who have been subject to inner ear radiation or who have undergone cisplatin or carboplatin chemotherapy, may report hearing loss depending on dosage (Doolittle et al. 2001; Schiffman 2007). Cisplatin in particular is used in the treatment of various kinds of cancers (ovarian, testicular, lung and also head and neck), and it may result in various degrees of hearing loss from 4 to 91 % (Doolittle et al. 2001; Yakirevitch et al. 2005).

Hearing loss is also an issue for nasopharyngeal carcinoma patients, especially those subject to radiation doses larger than 48 Gy (Gray, a unit of measurement of absorbed radiation) (Chen et al. 2006). Auditory problems can be particularly serious for cancer patients undertaking radiation therapy that involves the inner ear. Grau et al. (1991) studied 22 patients who had completed treatment for nasopharyngeal carcinoma and detected a dose-dependent reduction of hearing capability in patients exposed to radiation of the inner ear.

Touch

Although the sense of touch tends to decrease in effectiveness with age in perfectly healthy individuals (Schiffman 2007), it may also decrease prematurely as a result of disease. Abnormal performance of the sense of touch is known as *paraesthesia*,

and, among other causes, it could be a manifestation of some forms of cancer and its treatment. Peterson et al. (1994) describe how a sample of breast cancer patients displayed paraesthesia in the upper and lower limbs. A breast carcinoma patient was described by Bechich et al. (2000: 552) as showing “numbness and paresthesias in the toes and finger tips that progressed to involve all four limbs”. The same patient displayed not only an evident decrease in sensitivity to touch, especially in the distal parts of the four limbs, but also insensitivity to vibrations. Local loss of the sense of touch has also been associated with treatment of oral and pharyngeal cancer (Schiffman 2007). In general, paraesthesias can also develop as a result of chemotherapy (see Wickham (2007) for a review). *Chemotherapy-induced peripheral neuropathy* involving loss of sensitivity to touch is a side effect of the use of various types of drugs in chemotherapy (e.g. Wolf et al. 2008).

Temperature Sensitivity

As for the sense of touch, sensitivity to temperature also decreases with age in healthy people, especially towards the extremities (e.g. toes, fingers) (Schiffman 2007). However, it may also be affected by cancer. In particular, the experience of hot flushes, often associated with sweating, is common in breast cancer patients (around 65 % of survivors), a relationship that is only partially explained by therapy (Carpenter et al. 2004; Carpenter 2005). Men can also experience hot flushes as a consequence of some cancers (e.g. prostate). Janet Carpenter (2005 and references therein) lists the following behavioural effects of breast cancer-related hot flushes in women: increased depression, anger, tension, confusion, fatigue and sleeplessness. In men experiencing hot flushes consequent to prostate cancer, there may also be some associated effects on the quality of life.

Finck et al. (1998) studied hot flushes in 102 breast cancer patients. Most of the individuals in their study experienced hot flushes and listed some specific behavioural responses to flushes such as uncovering, drinking water and fanning. A total of 8 % of respondents also mentioned specific emotions associated with the hot flushes: annoyance, agitation, fatigue, irritation and embarrassment (see Table 2.12). Hot flushes were cause of interruptions of daily activities and also sleep disruption.

Hot flushes can also be an effect of chemotherapy (e.g. tamoxifen treatment) (Bruijs 2007).

Olfaction

Most people find the experience of eating pleasurable and rewarding. Although we obviously have a basic biological need to eat as this is the way in which we intake the basic nutrients that allow our organism to function, there is also a psychological dimension to eating. Good food can relax us, uplift our mind and spur our desire to communicate and share, as eating is often a social activity. On the other hand, unpleasant food can annoy and irritate. Although much time is devoted to visual

Table 2.12 Behavioural effects of hot flushes of various degrees of severity in breast cancer patients

Severity	Somatic sensation	Emotional perceptions	Associated behaviours
Mild	Warm, red face, uncomfortable	Unexpected	Usually none
Moderate	Warmth involving neck, ears, head, whole body, perspiration, clammy skin, dry mouth, tense muscles, tachycardia	Irritation, agitation, bothersome, annoying, tiring, embarrassing, memorable, energy, draining	Fanning, uncovering, drinking water, opening windows
Severe	Extreme warmth, weak, faint, headache, chest heaviness, extreme perspiration, prickling sensation over skin, heart irregularities	Anxious, panic attacks, embarrassment	Disrupted activities including sleep, inability to garden, removal of clothes, thermostat adjustments, movement, opening windows, use of fans
Very severe	Boiling eruptions, rolling perspiration, inability to breathe, faint/dizzy, leg/foot cramps, heart irregularities, nausea	Distressed, urge to run, difficulty functioning	Major sleep disturbance, clothes and bed linen changes, cold showers, use of ice, thermostat adjustments

Modified from Finck et al. (1998)

presentation of dishes, we mainly perceive the properties of food through the senses of smell and taste. Of course, smell and taste are also used to perceive properties of our environment other than food, but for cancer patients the issue of nutrient intake may become a very serious problem that requires specific attention. Smell and taste are distinct and yet closely intertwined as they are both activated simultaneously when we eat, and their combined action produces the sensation of *flavour*. Although for analytical purposes we will review them in separate sections, such interaction should be kept in mind.

We can smell following two different modalities: directly through our nostrils, referred to as *orthonasal olfaction*, or through the mouth that pushes chemicals—those present in the food for instance—towards the olfactory receptors through the action of chewing and swallowing. This is known as *retronasal olfaction* (Comeau et al. 2001).

As for other senses, the sense of smell can also change in cancer patients due to both the disease (in association with autoimmune syndromes, for instance (e.g. Moscovitch et al. 2009), which in turn can be a consequence of cancer development (e.g. Jones 1973)) and its treatment, whether such treatment is radiotherapy, chemotherapy or immunotherapy (Schiffman and Graham 2000; Schiffman 2007; Hong et al. 2009). Change may occur through a distorted perception of odours (*dysosmia*) or through alterations in the threshold levels that we can perceive: *hyperosmia* if we become more sensitive to odours, *hyposmia* if we are less sensitive and *anosmia* when we cannot differentiate any odour at all (Comeau et al. 2001). The ability to smell as well as to taste affects the palatability of food that, in turn, may compromise food intake with consequences on weight loss and key nutrient deficiency. A seriously malnourished body will be less likely to both fight the disease and withstand the side effects of therapy.

Cancer patients may also experience particular smells when thinking about specific past events; this is the so-called *phantosmia* (see Hong et al. 2009). Memories of staying in hospital may produce the perception of “hospital odours”, for instance, that could then be associated with nausea or loss of appetite.

In a study carried out on elderly residents in a retirement home, Schiffman and Warwick (1993) showed that when food such as vegetables, gravies, sauces, breakfast and main courses were enhanced by the addition of odours mimicking roast beef, ham, natural bacon, maple and cheese, with taste properties remaining unchanged, consumption of food increased. Interestingly, consumption of such odour-enhanced foods was also associated with increased levels of circulating T and B lymphocytes, an effect that was not explained by increase in consumption of micro- and macronutrients. The same result was obtained when food was enhanced by adding monosodium glutamate, which gives food a meat-like taste known by the Japanese word of *umami* (some people, however, are allergic to monosodium glutamate). Schiffman and Miletic (1999) showed that odour-enhanced food stimulates salivary secretion of IgA, a response that on the one hand indicates the degree of immune capability of the patient and on the other helps the patient defend the buccal epithelium against some potential infectious agents found in food.

The above evidence notwithstanding, we should also point out that people build up, throughout their lives, considerable knowledge about food and they construe an “odour repertoire” that may be significantly different from one ethnic group to another. The example above about the positive effect on consumption of food of adding bacon and roast beef odours to a dish may not be necessarily universal. The main point here is that regardless of the food that is preferred, patients’ appetite can be enhanced by the addition to food of those odours that are most appealing to them.

Cells of olfactory tissues are constantly regenerating and are sensitive to the effect of anti-cancer drugs such as cisplatin. As a consequence, cisplatin chemotherapy may be associated with alterations of the sense of smell. In a work carried out in Israel by Yakirevitch et al. (2005) they studied 13 male and 8 female patients being treated for various kinds of cancer (carcinoma, melanoma, breast, lung, cervix and others) with chemotherapy that in all cases included cisplatin in combination with other drugs depending on the specific type of cancer. The effect of treatment on olfaction was variable, with 1 patient showing decreased olfaction, but the remaining 20 did not have decreased olfactory capabilities; quite on the contrary, 10 patients in fact seemed to increase their olfactory abilities after chemotherapy. Yakirevitch et al., however, suspect that such improvement in those patients may be a result of learning effects.

Olfaction in nasopharyngeal carcinoma patients is negatively affected by radiotherapy, and oncological drugs such as *tegafur* are also cause of alteration in the sense of smell (Schiffman 2007 and references therein). Bernhardson et al. (2008) studied a group of 518 Swedish patients undergoing chemotherapy for various types of cancer; of those, 75 % reported chemosensory change during therapy, with 40 patients (7.7 %) describing changes in their sense of smell only. Young females tended to be more likely to experience sensory changes. In order of importance, changes occurred in the perception of the following smells: perfume, cooking, own body, hospital smells, someone else’s body, chemotherapy, automobile fumes and cleaning products.

From this we can conclude that when olfactory capabilities are altered as a consequence of cancer and/or its treatment, the well-being of the patient could be potentially affected through altered food consumption, especially when eating decreases. On the other hand, when the odour properties of food are enhanced, it could help the patient through not only improved consumption but also a specific improvement of immunocompetence.

Taste

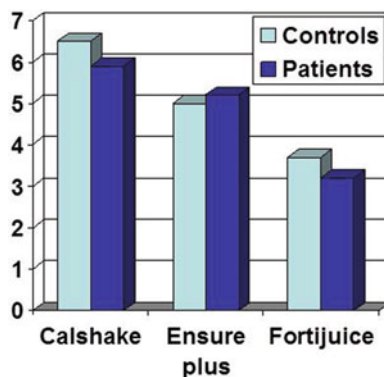
As for the case of smell, changes in the sense of taste (*dysgeusia*) due to direct effects of cancer, cancer therapy or both can also affect the ability of cancer patients to nourish themselves appropriately, leading to loss of weight when food does not taste good, with potential consequences for recovery (Schiffman and Graham 2000; Hong et al. 2009). Dysgeusia is common but variable across cancer patients, occurring in a range of between 15 and 100 % of cases across studies, with changes in taste tending to increase as the disease progresses (Ravasco 2005; Schiffman 2007 and references therein). In general, head and neck cancer patients are more likely to complain of changes in their taste perception (Hong et al. 2009). Most changes tend towards a decrease (*hypogeusia*) or an elimination (*ageusia*) of such taste perception capabilities that can be protracted for a few weeks to 6 months or even longer (Schiffman 2007). Such sensory changes have been associated with various degrees of malnutrition in about 40 % of cancer patients (Rahemtulla et al. 2005), whereas malnutrition significantly adds up to the effects of the disease in explaining the physical and mental deterioration of cancer patients (Hong et al. 2009).

Taste receptors are found in the tongue, palate and throat, and they are responsible for our salty, acid, bitter, sweet and umami perceptions, the latter being associated with detection of amino acids (Ravasco 2005). Sensory cells of the tongue have just a few days' lifespan and are fast reproducing; this makes them good unintended targets for drugs used in chemotherapy, which are designed to interfere with the fast-reproducing cancer cells.

In a study carried out in Sweden on children diagnosed with various forms of cancer, Skolin et al. (2006) found that change in taste was the most common cause associated with eating problems and intake of food; changes ranged from previously palatable food having a strange taste to being tasteless. The same authors also recorded cases of learned food aversions that developed because food was perceived as distasteful or because it was consumed when the child was also experiencing nausea following chemotherapy. Older children especially (8–17 years) had the greatest tendency to decreasing their food intake in hospital due to a negative perception of food taste: food was “disgusting”. Cancer patients in this study became less sensitive to bitter and salty tastes, but their ability to perceive sweet and sour tastes remained unaltered.

In a randomised double-blind study carried out in the UK, Rahemtulla et al. (2005) tested the palatability of three prescribable sip feeds: Ensure Plus (a milk-based, strawberry-flavoured sip feed), Fortijuice (a forest fruit-flavoured, fruit

Fig. 2.11 Preference mean scores for three food supplements by cancer patients and controls (redrawn from Rahemtulla et al. 2005)



juice-based sip feed) and Calshake (a strawberry-flavoured, fresh milk-based sip feed) in adult patients who were about to start chemotherapy for gastrointestinal cancer. A total of 47 patients and 47 healthy controls participated in this study until its completion. About a third of patients (30 %) indicated that they had experienced a change in taste perception since they had cancer but before starting their chemotherapy treatment. Patients with more advanced cancer were more likely to report changes in taste perception. Overall, both controls and cancer patients preferred Calshake to Ensure Plus and preferred the latter to Fortijuce (see Fig. 2.11). Although patients tended to prefer Calshake and Fortijuce slightly less than controls (Fig. 2.11), the differences were not statistically significant. In this case it seems that the specific effect of cancer and cancer therapy on palatability of those three common hospital food products is relatively minor.

Chemotherapy has been reported to affect the sense of taste in 36–75 % of cancer patients (Ravasco 2005). Various drugs can produce such an effect, including cisplatin, doxorubicin, carboplatin, cyclophosphamide, methotrexate and others (Comeau et al. 2001; Ravasco 2005; Yakirevitch et al. 2005). Such drugs produce experiences of depressed or enhanced basic taste perceptions affecting proper alimentation and quality of life.

Bernhardson et al. (2008) reported that 67 % of cancer patients in their study experienced changes in their sense of taste during chemotherapy. A total of 41 % of those patients modified their perception of salty foods, whereas changes in sweet perceptions were mentioned by 36 % of patients. Alterations in bitter perceptions were mentioned by 24 % of patients, and sour perception changed in 21 % of patients.

Differences in taste perceptions in cancer patients may be explained by physiological alterations of the tongue. In a study carried out on 110 adult cancer patients (68.1 % women) undergoing chemotherapy, Berteretche et al. (2004) recorded electric activity in the tongue using an “electrogustometer”, which simply measures the capacity of the patient to detect low-intensity electric currents in various parts of the tongue. Most control individuals had current detection thresholds below 30 μ A, whereas more cancer patients had thresholds above 30 μ A (24 %) compared to controls (10 %). That is, the tongue of cancer patients is relatively less sensitive to low-intensity currents than that of control individuals.

Table 2.13 Changes in threshold, intensity, discrimination and identification of taste experiences

Prior to therapy	Type of cancer	Effect of therapy	<i>N</i>
Elevated detection and recognition thresholds for NaCl (salty), sucrose (sweet), HCl (sour) and urea (bitter) prior to radiotherapy	Various malignant neoplasms	Salty, sweet and bitter further impaired by radiotherapy	35
	Oropharyngeal cancers	Elevated recognition thresholds for sucrose (sweet), HCl (sour) and quinine (bitter) during radiotherapy	8
	Head and neck	Elevated detection and recognition thresholds especially for bitter and salt thresholds during radiotherapy	13
Elevated NaCl (salty) recognition thresholds	Breast and colon		48
Elevated recognition threshold for hydrochloric acid (sour); individual differences in bitter and sweet threshold changes	Lung		30
	Oropharyngeal	Elevated taste recognition thresholds for NaCl (salty), sucrose (sweet), quinine sulphate (bitter) and picric acid (sour) during and after radiotherapy	1
	Oral squamous cell carcinoma	Thresholds for NaCl (salty), tartaric acid (sour), sucrose (sweet) and quinine (bitter) elevated by radiation and chemotherapy	41
	Various malignant neoplasms	Elevated glucose recognition threshold during chemotherapy	36
	Lung, ovary, breast	Thresholds decreased in patients who responded to chemotherapy	51
Significant increase in electrical taste detection threshold			
Significant decrease in recognition threshold for urea (bitter)	Gastrointestinal		30
	Melanoma	Loss of ability to discriminate between different concentrations of salt, sweet, sour and bitter during chemotherapy	?

N number of patients

Modified from Schiffman and Graham (2000)

Likewise, radiotherapy can also affect taste perceptions in cancer patients, especially when it is directly aimed at neck and head (Ravasco 2005). Radiotherapy may enhance or depress the ability to perceive various flavours, an effect that tends to be temporary unless radiation doses to neck and head are higher than 60 Gy, in which case the alteration may be permanent (Ravasco 2005).

Schiffman and Graham (2000) list a series of changes in taste perception that are due to cancer alone or therapy (see Table 2.13). The vast majority of cancer effects

Table 2.14 Management strategies to improve taste and smell alterations associated with cancer and cancer therapy

Avoiding the use of metallic silverware to reduce the risk of metallic taste
Reducing the consumption of foods that taste metallic or bitter, such as red meat, coffee or tea, and increasing the consumption of high-protein, mildly flavoured foods, such as chicken, fish, dairy products and eggs
Adding seasonings and spices to enhance flavours if hypogeusia or hyposmia is experienced
Serving foods at cold temperature to reduce unpleasant flavours and odours
Practicing good oral hygiene, including frequent tooth brushing and use of mouthwash
Using agents that stimulate salivary secretion, such as sugar-free gums or sour-tasting drops

Modified from Hong et al. (2009)

are to impair the sensory ability to perceive salty, sweet, sour and bitter tastes. Chemotherapy and radiotherapy further decrease such sensory capabilities.

Consequent to the taste changes listed in Table 2.13, Schiffman and Graham (2000) also reported a series of altered food preferences ranging from reduced palatability and feeling of nauseating tastes, leading to food aversions and reduced appetite but also some instances of food cravings.

Change in taste perception among cancer patients may be associated with depression, especially as a direct result of loss of the pleasure that is usually derived from eating a preferred meal (Ravasco 2005 and references therein). However, and perhaps even more dramatically, changes in taste sensory capabilities may lead to food aversion that could derive into malnutrition. This is especially important when aversion is for important dietary items such as proteins (e.g. meat) or vitamins (e.g. citrus, vegetables in general). This leads to the need to design effective strategies to increase palatability of food; such strategies, however, will require a compromise between medical needs and personal preferences of the patient.

Given the potential negative effects of an altered sense of taste and also smell associated with cancer and cancer therapy, some recommendations have been suggested to help decrease those effects to some extent. Table 2.14 provides a list of such recommendations following Hong et al. (2009).

In sum, cancer and cancer treatment may alter our sensory capabilities and such alterations could affect behaviours and the quality of life of patients, especially when food consumption is modified. If this happens, our body's ability to fight the disease may be compromised. Behavioural strategies to improve food consumption in cancer patients are suggested, but individual tailoring of sensory interventions is recommended.

Summary of Main Conclusions

- Cancer is an ancient family of diseases of humans and other animals that affect the ability of cells to operate as functional parts of an organism. Cancerous cells reproduce unchecked potentially leading to the death of the organism in the most extreme of cases.

- The *sickness syndrome* is characterised by a series of behaviours adopted by animals and humans under the stress of disease, including those suffering from various forms of cancer. Such behaviours are adaptations against disease, but they could derive into more psychopathological states such as depression. The sickness syndrome is the result of multiway interactions between the nervous, immune and endocrine systems, with inter-systemic communication being facilitated by molecules such as the cytokines.
- Behaviour could have an effect in mediating both promotion of cancer (e.g. stressful experiences that may affect the rate of mutation, methylation, apoptosis and immune dysregulation) and defence against cancer (e.g. relaxation that provides relief from stress). Effects of psychological stress on hormones, cytokines, ROS and telomere length may increase the probability of cancerous mutations, whereas alterations in the patterns of DNA methylation may promote cancer via epigenetic mechanisms.
- The experience of a cancer patient may be described through a series of phases that starting from a perception of feeling unwell may take the patient through a medical visit, a diagnosis, treatment and prognosis, follow-up visits, remission, potential recurrence and potential end-of-life process in the most extreme of cases. In each one of those phases, issues of feelings, thoughts and communication can be important in understanding both the progression of the disease and the ability of the patient to fight back. The feeling of distress is clearly one of the first emotions experienced by the patient that may be counteracted by activating effective coping strategies.
- Pain that is often experienced by cancer patients involves physiological, sensory, behavioural, affective, cognitive and sociocultural dimensions. Although the pain experience could be modulated by the patient through catastrophising to extract more assistance from his/her social environment than is probably required, caregivers should be wary not to push this possibility too far, as neglect of physiological pain with a direct cancer aetiology may jeopardise treatment and patient's well-being.
- Fatigue is one of the most common effects of cancer and its treatment. It can affect daily activities through modifying mental performance and social interactions. Cancer-related fatigue is most likely mediated by the activity of cytokines.
- Cancer patients may suffer from altered patterns of sleeping. Insomnia in particular is a common condition associated with various forms of cancer. CBT have been developed to deal with insomnia, and their use may help the patient to gradually improve his/her sleeping routine. Cytokines seem to provide a molecular link between cancer and sleeping behaviour.
- Changes in light/darkness cycles—such as those associated with specific jobs—and various kinds of stresses, including social stresses, may alter the activity of the suprachiasmatic nucleus in the brain that in turn affects the usual operation of various parts of the nervous system, including the hypothalamus and the pineal gland. This in turn leads to changes in the production of melatonin and steroid hormones that can finally affect the activity of the immune system, thus compromising the body's ability to defend itself against tumours.

- Nausea is a common experience of cancer patients. It may be caused by cancer itself and/or by treatment. From a psychological perspective, nausea may affect and is being affected by cognitive, emotional and personality characteristics of the patient.
- Cancer and cancer treatment may also alter our sensory capabilities, and such alterations could affect behaviours and the quality of life of patients, especially when food consumption is modified. If this happens, the body's ability to fight the disease may be compromised.

In the next chapter we explore various important psychological effects of cancer that include depression, emotions, cognition and memory. Changes in sexual behaviour and personality characteristics will also be analysed in cancer patients and how they are modulated by gender and age.

Topics for Discussion

1. Modern lifestyles may favour the development of cancer through exposure to mutagenic chemicals or radiation but also by compromising our immune system through diet and stress. Simple lifestyle changes may achieve great results in terms of cancer prevention. Discuss the behavioural and cultural obstacles that can interfere with the adoption of such lifestyle changes.
2. If the sickness syndrome is an evolved strategy to cope with disease, at which point should we intervene to eliminate the various behaviours characteristic of the syndrome, and when should we allow them to freely express themselves?
3. Some cancer patients at their early stages of cancer development may benefit from “fighting spirit”. Think of psychological interventions for cancer patients to enhance their “fighting spirit”. What kind of obstacles could limit the effectiveness of such interventions? Even at the early stages of cancer, how would you address a cancer patient who is uninterested in concepts such as “fighting spirit”? How would you contextualise “fighting spirit” given the prospect that oncological treatment may not be successful?
4. On the basis of the information available in Table 2.10, what kind of psychological strategies would you use to modify the perception of pain by cancer patients? How would you deal with a catastrophising patient?
5. What kind of menu would you design for a cancer patient who is suffering from nausea and has a partially impaired perception of flavour?

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