Dear Zoe

Thank you for your email. I apologise for not responding to your earlier communication, it must have gone ‘hull down’ amongst the hundreds of emails I get each week. I support the petition. I append some papers which we have published in the recent past in connection with cancer and the environment, in evidence.

In particular I would like to draw your attention to the paper on the ‘cancer temporality index’. I note that one of the responses to the petition wheels out the weary old argument the ‘we are getting older and therefore the incidence of cancer must increase’, as if simply getting older is the cause of the cancer. Of course if you exist in an environment that is full of cancer causing agents/influences, age will be one of the functions associated with cancer because the longer you live the more time such influences have to act. In the cancer temporality index paper we demonstrate that, for some cancers, the average age of incidence is decreasing – people are getting cancer younger. This does not fit in with the ‘we are getting older’ argument.

I hope that these submissions will help the Committee in its deliberations.

With best wishes

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Dossier : Cancer : Influence of environment

Lifestyle-related factors and environmental agents causing cancer: An overview

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Received 4 October 2007; accepted 10 October 2007
Available online 20 November 2007

Abstract

The increasing incidence of a variety of cancers after the Second World War confronts scientists with the question of their origin. In Western countries, expansion and ageing of the population as well as progress in cancer detection using new diagnostic and screening tests cannot fully account for the observed growing incidence of cancer. Our hypothesis is that environmental factors play a more important role in cancer genesis than it is usually agreed. (1) Over the last 2–3 decades, alcohol consumption and tobacco smoking in men have significantly decreased in Western Europe and North America. (2) Obesity is increasing in many countries, but the growing incidence of cancer also concerns cancers not related to obesity nor to other known lifestyle-related factors. (3) There is evidence that the environment has changed over the time period preceding the recent rise in cancer incidence, and that this change, still continuing, included the accumulation of many new carcinogenic factors in the environment. (4) Genetic susceptibility to cancer due to genetic polymorphism cannot have changed over one generation and actually favours the role of exogenous factors through gene-environment interactions. (5) Age is not the unique factor to be considered since the rising incidence of cancers is seen across all age categories, including children, and adolescents. (6) The fetus is specifically vulnerable to exogenous factors. A fetal exposure during a critical time window may explain why current epidemiological studies may still be negative in adults. We therefore propose that the involuntary exposure to many carcinogens in the environment, including microorganisms (viruses, bacteria and parasites), radiations (radioactivity, UV and pulsed electromagnetic fields) and many xenochemicals, may account for the recent growing incidence of cancer and therefore that the risk attributable to environmental carcinogen may be far higher than it is usually agreed. Of major concern

Abbreviations: CMR, carcinogenic, mutagenic and reprotoxic; CYP450, cytochrome P450; DEHP, di(2-ethylhexyl)phthalate; DNA, deoxyribonucleic acid; EBV, Epstein–Barr virus; EMF, electromagnetic fields; ELF, extremely low frequency; ETS, environmental tobacco smoke; HBV, hepatitis B virus; HCB, hexachlorobenzene; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HD, Hodgkin’s disease; HIV, human herpes virus; HBV, human immunodeficiency virus; HNPPC, hereditary non-polyposis colorectal cancer; HPV, human papilloma virus; HTLV-1, human T-cell lymphotropic virus type 1; IARC, International Agency for Research on Cancer; INSEE, Institut National de la Statistique et des Etudes Economiques; InVS, Institut national de veille sanitaire; KS, Kaposi sarcoma; MRI, magnetic resonance imaging; NCI, National Cancer Institute, USA; NHL, non-Hodgkin lymphoma; NOC, N-nitroso compounds; OECD, Organization for Economic Cooperation and Development; PAF, population attributable fraction; PAH, polycyclic aromatic hydrocarbons; PCB, polychlorinated biphenyls; POP, persistent organic pollutants; PVC, polyvinyl chloride; RNA, ribonucleic acid; SEER, surveillance, epidemiology and end results; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; UADT, upper aerodigestive tract; US EPA, US Environmental Protection Agency; UV, ultraviolet; VLF, very low frequency; VOC, volatile organic compounds; WHO, World Health Organization.

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0753-3322/S - see front matter © 2007 Elsevier Masson SAS. All rights reserved. doi:10.1016/j.biopha.2007.10.006
are: outdoor air pollution by carbon particles associated with polycyclic aromatic hydrocarbons; indoor air pollution by environmental tobacco smoke, formaldehyde and volatile organic compounds such as benzene and 1,3 butadiene, which may particularly affect children and food contamination by food additives and by carcinogenic contaminants such as nitrates, pesticides, dioxins and other organochlorines. In addition, carcinogenic metals and metalloids, pharmaceutical medicines and some ingredients and contaminants in cosmetics may be involved. Although the risk fraction attributable to environmental factors is still unknown, this long list of carcinogenic and especially mutagenic factors supports our working hypothesis according to which numerous cancers may in fact be caused by the recent modification of our environment.

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Keywords: Air pollution; Alcohol; Ageing; Cancer; Carcinogenesis; Diet imbalance; Dioxins; Environment; Fetus susceptibility; Food additives; Food contaminants; Genetic susceptibility; Nitrates; Obesity; Pesticides; Radiations; Screening; Tobacco smoking; Viruses

1. Introduction

Lifestyle-related factors are not by themselves cancer causing agents, but are risk factors associated with the genesis of cancer, through professional exposures, behavior-related habits and addiction leading to exposure to recognized or suspected carcinogens. While lifestyle-related factors are usually well-determined and thus accessible to epidemiological studies, cancer causing agents, because they are multiple, diverse and diffuse in the environment, are more difficult to identify and recognize and therefore evidence through classical epidemiological methods. Indeed, in the case of environmental carcinogens, we need to not only analyse the results of epidemiological studies, but also consider biological and toxicological data in close relationship with genetic susceptibility in the context of molecular gene–environment interactions, in order to interpret epidemiological studies in a more comprehensive way.

There are currently two opposite interpretations of the growing incidence of cancer. The first one considers that environmental pollutants can only make a minor contribution to the overall cancer incidence changes and therefore that increase in the size and ageing of the population, lifestyle influences such as smoking, alcohol consumption and diet, and new progress in diagnosis and screening procedures can explain most of the current increased cancer incidence [1—3]. Conversely, the second interpretation, considering that these arguments are not sufficient, estimates that in addition to these factors, there is a contribution from the environment and that involuntary exposure to diverse physical, chemical and biological agents, which may be present in the surroundings of individuals play a major role in the occurrence of the disease [4—8].

In a previous paper, we have shown that lifestyle-related factors, as well as ageing and new diagnostic and screening tests, cannot fully account for the overall recent growing incidence of cancer in the Western countries [9]. Moreover, we have proposed a hypothesis according to which the involuntary exposure to environmental carcinogens could contribute to the growing incidence of cancer in Western countries and, in a more recent paper, we have suggested that environmental carcinogens may in fact play a more important role in carcinogenesis than it is usually agreed [10].

In this paper, we intend to further show that studies of lifestyle-related factors are unsuccessful to fully understand the recent growing incidence of cancer and that cancer causing agents as evidenced from toxicological and biological investigations must be taken into account to interpretate correctly both carcinogenesis and current public health concerns.

2. Lifestyle-related factors

It is well agreed that smoking and to a lesser extent alcohol consumption, diet imbalance, obesity and lack of physical exercise can contribute to cancer in high-income countries.

2.1. Tobacco smoking

Smoking is indeed a serious concern, and a major risk factor contributing to human carcinogenesis (Table 1). Because tobacco smoke and tar contain thousands of compounds including many mutagens such as polycyclic aromatic hydrocarbons (PAH) and nitrosamines and as well as other promoters, this mixture constitutes the equivalent of what is defined as a complete carcinogen [9]. As underlined by many authors, smoking is a risk factor for several types of cancers, mainly lung cancer and cancers of the upper aerodigestive tract (UADT), and also, to a certain extent, for esophagus, stomach,

<table>
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<tr>
<th>Cancer Site</th>
<th>Men (%)</th>
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<td>Alcohol-related cancers</td>
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<tr>
<td>Oropharynx</td>
<td>21</td>
<td>8</td>
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<tr>
<td>Oesopharynx</td>
<td>14</td>
<td>6</td>
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<td>Liver</td>
<td>18</td>
<td>12</td>
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<td>Larynx</td>
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<td>Female breast cancer</td>
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<td>Pancreas</td>
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<td>Cervix</td>
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<td>Vulva</td>
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<tr>
<td>Penis</td>
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<tr>
<td>Bladder</td>
<td>43</td>
<td>36</td>
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<tr>
<td>Renal parenchyma</td>
<td>28</td>
<td>21</td>
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<tr>
<td>Renal pelvis</td>
<td>55</td>
<td>48</td>
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</tbody>
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Table 1 Percentage of cancers attributable to alcohol and smoking according to English et al. 1995 [11]
pancreas, liver, bladder, kidney and cervical cancers, as well as myeloid leukemia [11,12]. Because many of these cancers are associated with a poor prognosis, smoking remains a major cause of cancer mortality. In high-income countries, the mean population attributable fraction (PAF) for tobacco smoking in both sexes combined is estimated to be 25–30% of the overall cancer mortality [13]. However, because many common cancers not usually related to smoking have generally a lower lethality the PAF related to the overall cancer incidence is lower than for mortality probably in the order of 20–25% [7].

2.2. Alcohol consumption

In contrast with PAH and other carcinogenic molecules found in tobacco smoke and tar, ethyl alcohol is not per se mutagenic, but rather acts mainly as a cocarcinogen. On the basis of epidemiological data, alcohol has been classified as a human carcinogen [14]. Indeed alcohol can potentiate the carcinogenic effects associated with smoking or other factors [15], but overall its action is not clear. Indeed, in addition to its predominant cocarcinogenic effect, ethanol has been thought to be associated with some promoting effect. Here we clearly distinguish cocarcinogens from promoters. A cocarcinogen is a molecule which can activate or enhance the action of a carcinogen, be it a mutagen or a promoter [16]. On the other hand, a promoter is a molecule which stimulates the division of cells and may facilitate loss of differentiation and apoptosis induction, whether the cells are mutated or not [9,17]. Among the cocarcinogenic effects of alcohol are the depletion of detoxifying molecules such as glutathione and the induction of the hepatic cytochrome P450 2E1 (CYP2E1) enzyme, leading to the activation of procarcinogens into carcinogens [18,19]. By contrast, a promoting effect for alcohol through immunosuppression induction has been suggested [20]. However, this hypothesis has never been validated through pertinent toxicological and epidemiological studies. In addition, because induction of CYP2E1 in the liver may result in ethanol metabolising into acetaldehyde, thus leading to the production of some mutagenic free radicals, it has been postulated that ethanol may also play a role in cancer initiation, and especially contribute to initiate hepatocellular carcinoma (HCC) through mutagenesis [21]. Yet, this hypothesis supported by some animal experiments needs to be validated. Furthermore, due to a decrease in alcohol consumption over the last 20 years, PAF for alcohol-related cancers is only 4% in high-income countries, yet much higher in men than women [22]. We therefore conclude that the mechanism of the carcinogenic effect of ethanol needs to be clarified by new toxicological, biological and epidemiological data, and that overall, because of the decreasing alcohol consumption it cannot account for the recent growing incidence of cancers.

2.3. Diet

Several studies have shown that in highly developed countries, food intake imbalance, rich in calories and animal fat and low in fibre, in other words, rich in red and processed meat and poor in fruits and vegetable, is a factor that fosters the occurrence of some cancers (colon, prostate, endometrium and breast) and conversely that a high intake of fruits and vegetables has a protective anticancer effect [23,24]. Migrants’ studies strongly suggest that lifestyle-related diets can affect promotion of the aforementioned cancers [25–28]. A common interpretation is that increased animal fat intake, rich in polyunsaturated fatty acids, can generate mutagenic free radicals by increasing oxidative stress [29], while diets rich in fruits and vegetables, because they contain many natural antioxidants, can yield anticancer protection [30–32]. We have questioned the magnitude of these presumed effects and challenged the common interpretation assuming that diet per se, i.e. food intake imbalance alone could be a risk factor of cancer. Indeed, the PAF for cancers related to low fruit and vegetable intake is estimated to be only 3% of the cancer mortality in Western countries [22]. In addition, from experimental animal studies, it has never been proven that high fat diet can initiate cancers, but rather that fatty diets can be associated with a cocarcinogenic effect through the induction of the cytochrome P450 system [33]. Furthermore, on the basis of epidemiological and biological data, the role of dietary fat in carcinogenesis is not clear. Many epidemiological studies testing the presumed role of animal fat in the genesis of cancer are controversial [34–36]. A limitation could be that these studies have not been evaluated by taking into account genetic polymorphism and/or continuous induction of CYP450 together with the duration of exposure. Although it has been shown that animal fat intake may be associated with colorectal cancer occurrence, it has never been proven that fat per se can initiate carcinogenic effects [37,38]. Yet, more attention should be devoted to the effects of diet at different periods in life, in utero and most importantly peripuberal periods having the potential for being windows of susceptibility [Sasco AJ, Besson H, Little RE. Dietary habits during childhood and adolescence and breast cancer risk. In: Bruni V, Dei M, editors. Pediatric and adolescent gynecology. Rome: CIC Edizioni Internazionali; 2003. p. 178–85.].

2.4. Overweight, obesity and sedentariness

Overweight, obesity and sedentariness have been incriminated as risk factors for cancer [39,40]. Recent studies in the USA have suggested that obesity associated with some cancers can worsen cancer mortality [41]. Indeed, because obesity is associated with diabetes mellitus and cardiovascular diseases, and thus can increases overall mortality, these studies do not prove that obesity per se is a factor involved in cancer mortality. However, in many studies, obesity was found to be associated with an increased incidence of several cancer types [42,43] with the exception of lymphoma [44] and childhood cancers [45]. Consequently, aside from these cancers, a recent hypothesis is that the observed increase of incidence of several cancer types, such as breast, endometrium, colon, liver or kidney cancers, may be related to obesity [46]. However, in the Western countries, the PAFs for
obesity-associated cancers and for cancers associated with physical inactivity are only 3% and 2%, respectively, for cancer mortality [22]. Thus, as for fatty diets, the role of obesity in carcinogenesis is not clear. Indeed a promoting mechanism whereby obesity could be a risk factor through a modification of the hormonal milieu remains hypothetical [40]. Moreover, it has never been demonstrated that excess weight and obesity in isolation can initiate cancer. They can, however, indirectly contribute to cancer genesis through a progressive accumulation of environmental chemical carcinogens in the adipose tissue. We have clearly shown that lipophilic organic xenomolecules such as benzo[a]pyrene can accumulate in adipose tissue [47] and therefore, that this tissue must be considered as a reservoir for lipophilic xenonmolecules including persistent organic pollutants such as dioxins and PCBs and many other carcinogenic, mutagenic and/or reprotoxic (CMR) products, including pesticides and/or other endocrine disrupting agents [48,49]. So, as a result of bioaccumulation and toxicity of these molecules in the adipocytes, and consequently death of adipocytes through apoptosis or necrosis, leading to the release of toxic compounds into the plasma, where they are detected [50]. Furthermore, we have clearly demonstrated that benzo[a]pyrene can favour obesity in mice by impairing β-adrenergic stimulation of adipose tissue lipolysis [48]. We therefore hypothesize that some carcinogenic molecules may be involved both in obesity and in cancer genesis [51]. Since obesity has been found to be associated with several types of cancer, our observation allows considering that factors other than food intake imbalance and abnormal diet may be involved in carcinogenesis. A large number of molecules, rated as carcinogenic, probably carcinogenic or possibly carcinogenic to humans, belonging respectively to the IARC’s groups 1, 2A and 2B for the evaluation of carcinogenicity to humans, can bioaccumulate in the organism and may contribute to carcinogenesis. We are therefore led to the conclusion that, in addition to classical lifestyle-related risk factors, other carcinogenic factors found in the environment could also play a role in the genesis of cancers.

2.5. Decrease in tobacco and alcohol consumption

Doll and Peto’s estimations on the attributable fractions of cancer dates back to 1981 and is based on earlier US epidemiological data, limited to white men younger than 65 years of age [52]. Yet, then our environment has been greatly modified. Alcohol consumption has been declining in all Western countries except in the Nordic ones, so it cannot explain the growing incidence of cancers in non-Nordic countries. In addition, the number of men who smoke decreased in several Western countries [9], so it cannot be a further explanation of the growing incidence of cancer in men, whereas it remains a major factor in countries of the south Europe and still in women in most parts of the world. Though mortality due to lung cancer has increased in men since the last world war in many countries and more recently in women, at the same time tobacco consumption and the proportion of regular smokers have decreased in men in several developed countries, whereas it has progressively increased in women [53]. This observation is worth discussing. The analysis of Fig. 1 shows that in France, the increase in mortality due to lung cancer in men slowed down since 1990 and currently tends to level off, which suggests that mortality could drop sharply in the years to come, if a stringent policy against smoking is maintained, as any epidemiological translation of reducing smoking requires decades before its health impact becomes fully apparent. This is indeed the case today in countries that have launched a real fight against smoking many years ago. However, because the PAF for tobacco smoking-associated lung cancer mortality is approximately 90% for men and 70% for women in industrialized countries [54] and possibly lower for its incidence, i.e. in the order of 80% and 60% respectively, it clearly appears that lung cancers are not exclusively related to tobacco smoking [55,56]. Likewise, recent epidemiological data concerning cancers partially related to tobacco smoking, such as bladder and renal cell carcinoma, need to be interpreted in the light of other causal factors. While over the last two decades the incidence of bladder cancer is decreasing in the UK, possibly because of a reduction of smoking, paradoxically it is increasing in France and is stable in the USA, although smoking is also decreasing, there at least in men [9]. A similar trend is observed with renal cell carcinoma. Incidence is growing in the UK, France and in the USA [9]. This strongly suggests that for kidney carcinoma as well as for bladder carcinoma, carcinogenic factors other than smoking have recently emerged [9]. A similar paradoxical picture exists for HCC. Although the incidence of UADT and esophageus alcohol-related cancers has markedly declined over the past decades in many European countries including France (Table 1, Fig. 2), mainly due to a decrease in alcohol and tobacco consumption, the incidence of HCC has increased. The currently growing incidence of HCC could therefore be the consequence of other oncogenic factors, such as viral hepatitis B and C [57,58] and/or chemical carcinogens [59,60], beside a potential role for better diagnosis.

Finally, a basic observation is that the incidence of and mortality from cancers strongly related to tobacco and/or alcohol consumption have been decreasing over the last two decades, while the incidence of cancers not related to tobacco...
and/or alcohol consumption or to obesity has been increasing (Fig. 3). This figure reversal characterizes many industrialized Western countries in Europe and in the USA, where the incidence of cancers non-related or weakly-related to alcohol and/or tobacco consumption is increasing [61,62]. This mainly concern breast cancer in women and prostate cancer in men, and also thyroid cancer, as well as some other cancers including melanoma, mesothelioma, brain tumors, leukemias and lymphomas in the adults of both sexes, as well as testicular cancers in young men and childhood cancers (Fig. 4).

2.6. Impact of new diagnostic and screening methods

Over the last two decades, in Europe and North America, the mean estimated number of yearly cancer cases has approximately doubled breast cancer [63,64], and more or less doubled for prostate cancer [64,65] and thyroid cancer [66]. Simultaneously, progress has been achieved in diagnostic and screening techniques including mammography for breast cancer, cervical smears for cervical cancer, PSA for prostate cancer and ultrasonography for thyroid cancer allowing detection of small tumors for these four cancer categories [67–70]. Clearly, the marked rise in the incidence of these cancer with the exception of cervical cancers which has drastically declined over the last decades [71] may be due in part to the detection of latent tumors which may have never progressed into symptomatic cancers. This effect is most likely for prostate and thyroid cancers [66,72,73]. However, although this incidence increase can be partly explained through the recent generalization of screening tests, we assume that in addition other factors do occur for the following reasons: (1) with the exception of some very slightly invasive and slowly progressing cancers, any truly invasive cancer almost always converts into a symptomatic disease and consequently is recognized clinically. A significant number of cancers for which no screening methods existed 30 years ago was thus probably clinically diagnosed, meaning that in the case of good cancer registries, there cannot have been a deficit in reporting in the past; (2) The current screening tests improve early detection of cancers and thus most probably improve prognosis. Indeed, screening for cancers which are detected at an already invasive stage (breast cancer for example) can only influence mortality. On the other hand, the impact on reduced incidence can only be assumed for cancers screened at a pre-invasive stage (cervix and colon cancers for example). The current tests should therefore influence mortality more than incidence unless one considers the possibility of numerous false positive tests, a hypothesis which warrants further investigation even in the case of histological confirmation with tissue biopsies showing invasive cancers. This is the case in particular for prostatic cancer. Careful analysis of biopsies revealed that screened cases were associated with the same Gleason grading as non-screened cases, meaning that screened cases may carry the same histoprognosis as non-screened cases [69] although the use of more refined biological markers could nuance that picture; (3) Consequently, as a result of screening, a clear decrease in mortality in countries that systematically used screening tests should have been expected. Unfortunately, except for cervical cancer, this is not the case. So, for breast carcinoma, since the use in the 1990’s of opportunistic and later organized screening in 16 European countries, where cancer incidence was increasing, cancer mortality was either stable or only slowly decreasing [74]. This indicates that part of the increased number of new screened cases was probably related to truly malignant cancers and that the screening methods are not sufficient to eradicate cancer mortality. This emerging new concept has been recently debated [75,76]. In fact, screening can influence mortality through the detection of both invasive cancers and pre-cancerous lesions [77,78]. This indicates
that screening may not as efficient as originally thought and that the growing incidence of cancer is not solely related to pre-cancerous or smoldering invasive cancers, but also to truly malignant cancers [79]; (4) In countries or regions where the incidence rates of breast, prostate or thyroid cancers have been historically low and where there has been no systematically performed screening, increased incidence rates of these cancers are now observed [25,65,80]; (5) In many countries, the increased incidence of these cancers is such that it is very unlikely that all new cases could be solely due to improvements in diagnosis, screening test procedures and data reporting (Figs. 4, 5); (6) A careful analysis of the cancer registries of countries that have systematically collected all new cancer cases during a sufficiently long period, i.e. before and after the introduction of new screening tests, supports this hypothesis: this is the case in Norway. Fig. 6 relates to the evolution of incidence rates for

Fig. 4. Incidence and mortality rates for different cancers (breast, prostate, bowel and brain and CNS) in UK in 1975–2003 (adapted from Cancer Research UK).

Fig. 5. Incidence and mortality rates for different cancers (NHL and leukemia) in UK in 1975–2003 (adapted from Cancer Research UK). Incidence and mortality rates for cancers in children and adolescents under the age of 20 in USA (1980–2000) (adapted from Ref. [64]).
suppressor, DNA repair and cancer susceptibility genes has within a stem cell [81]. The discovery of oncogenes, tumor involving accumulation of a critical number of mutations

2.7. Genetic versus environmental influences

of view. A biological, epidemiological, medical and public health point of view. Therefore, we theorize that the increased risk of cancer corresponds to a genuine phenomenon from a biological, epidemiological, medical and public health point of view.

2.7. Genetic versus environmental influences

Cancer is generally recognized as a multistage disease involving accumulation of a critical number of mutations within a stem cell [81]. The discovery of oncogenes, tumor suppressor, DNA repair and cancer susceptibility genes has led to the concept that carcinogenesis is a pure endogenous genetic process [82,83]. Clearly, this concept has to be revised, because causation of cancer must be distinguished from its consequences, i.e. the disease itself. Indeed, it has become increasingly evident that due to gene-environment interactions [84], cancer is causally partly an environmental disease. Two elegant studies documented this new scientific paradigm. Data based on the analysis of co-occurrence of cancer in a cohort of identical twins have demonstrated that environmental rather than genetic factors predominate in the aetiology of cancer. Theoretically a high level of co-occurrence would have revealed that inheritance is more influential than environmental factors in the causation of cancer. But this is not the case. The study showed that the concordance rate of cancer among identical twins was rather low, indicating that non-genetic influences predominate [85]. Moreover, estimation of the relative proportion of genetic and environmental influences for each specific cancer, using a structural equation model, showed that for all cancer types, except thyroid cancers, environmental factors (including lifestyle factors) predominated [86]. It appears therefore that environmental factors prevail in the aetiology of cancers and consequently that inherited genetic factors are not involved to any significant extent in the current growing incidence of cancer.

2.8. Innate and acquired susceptibility to cancer

In order to further examine the hypothesis according to which endogenous factors could be considered, it is necessary to question whether the growing incidence of cancer may have resulted from the occurrence of specific inherited mutations of susceptibility genes or from the acquired somatic susceptibility within the general population. It is clearly established that in addition to their mutagenic effects, radiation, viruses and chemicals can be cancer promoters in particular via immuno-suppression induction. Such a mechanism of acquired susceptibility to cancer is exemplified in selected specific population groups including patients treated with immunosuppressive drugs for organ transplantation [87–90], irradiated people [91,92] or people with HIV infection [93]. We do not know to what extent environmental immunosuppressive factors and particularly immunosuppressive chemicals could contribute to acquired susceptibility to cancer within the general population and therefore to what extent, these acquired environmental factors may have been implicated in the current growing incidence of cancer. On the other hand, inherited factors accounting for cancer susceptibility include theoretically specific oncogenes as well as genes involved in the activation or detoxification of carcinogens and repair of DNA damage [84]. In fact, three types of arguments discredit the hypothesis according to which an increase in inherited genetic susceptibility could have occurred, accounting for the growing incidence of cancer. (1) Only a small proportion of cancer follows a Mendelian pattern of inheritance [94,95]. Familial cancers arising as a result of highly penetrant mutations, be they associated or not with hereditary cancer predisposition syndromes, are
unlikely to account for more than 10–15% of all childhood cancers meaning that they represent no more than a few percent of the total cancer burden [96,97]. In addition, inherited tumor suppressor oncogenes, such as BRCA1 and BRCA2 genes, in patients with familial breast carcinoma [98] or other inherited susceptibility genes, such as hMSH2, hMLH1, hPMS1, hPMS2 and hMSH6 genes, in hereditary non-polyposis colorectal cancer (HNPCC) [99] are relatively rare in the general population although they may be more frequent in specific ethnic groups [100] and taken together account for less than 5% of cancers [101]. Moreover, despite considerable efforts to identify common less penetrant susceptibility genes for cancer, discovery of such genes is so far disappointing [102]. (2) By contrast, a more likely situation is that cancers develop as a result of exposure to risk factors in genetically susceptible individuals [103]. Indeed, inherited genes that encode enzymes involved in the activation or detoxification of exogenous carcinogenic factors are much more frequent. These genes are polymorphic in nature, meaning that they are a common variant of the enzymes’ genes [84,104]. As a consequence of polymorphism, individual variations in the metabolism of carcinogens account for differences in the susceptibility to cancer and could thus impact on the population attributable risk for cancer. Polymorphism has resulted from mutations, which have survived and passed through generations [84]. However, it is theoretically and practically impossible to believe that in one generation (25 years), genetic polymorphism would have been modified in such an extent that it could have increased so greatly the population’s genetic susceptibility [95]. (3) Moreover, while the rare childhood cancers associated with the Mendelian pattern of inheritance are purely related to the inherited penetrant endogenous mutations, for all the other inherited cancers, genetic susceptibility increases the risk of cancers related to exogenous and especially environmental factors [85,105]. For example, this is the case for women having mutated BRCA1 or BRCA2. The risk of having breast cancer at age 50 is 24% for those born before 1940, while it is 67% for those born later [98]. This means that since the last world war, a new phenomenon occurred, whether it is related to lifestyle modifications (hormone treatments, later age at first pregnancy, increased nulliparity etc.) or to environmental changes.

2.9. Ageing and extended life expectancy

A major and recurring counterargument to the environmental concept whereby the current growing incidence of cancer is due to changes in our environment is that we are living longer and cancer incidence increases with age. There is no doubt that life expectancy has been increasing for many decades in the Western countries and that cancer incidence increases with age, thereby leading to an increased number of new cases and of deaths from cancer [106–112]. The widely accepted opinion according to which extended life expectancy, i.e. increased age, is a major factor to explain the current increase in cancer incidence needs however to be clarified. Crude numbers of cancer burden, be it the number of new cases or the number of deaths, are affected by changes in the population size and structure. For comparisons of populations over time, age-standardized rates need to be computed. Therefore age no longer plays a role when examining age-standardized rates and their trends over time or differences across populations. A similar consideration applies to the comparison over time of age-specific rates. Changes in particular among young people are most informative. The role of ageing in the occurrence of cancer needs to be discussed from a biological standpoint. A basic assumption, which supports the role of age, is that, according to the multistage theory proposed by Armitage and Doll in 1954 [113], people living longer have a greater chance of accumulating the critical number of mutations needed for cell transformation. Indeed the multistage somatic mutations theory is not incompatible with the rising incidence of cancer associated with increasing age, if we assume that many environmental factors are carcinogenic and cancer risk is clearly related to the duration of exposure to exogenous carcinogens. However, in addition to this theory, a second hypothesis has been put forward indicating that besides the extended life duration, ageing by itself could favour cancer, meaning that in addition to mutations induced by exogenous factors, ageing-related endogenous mutations could occur. Consequently, it has been postulated that the currently expanded ageing of the population could be per se a major cause of the observed increased incidence of cancer. In fact it cannot be assumed that ageing by itself is a major contributing factor to cancer genesis for the following three reasons: (1) in tissue culture, there is no evidence showing that spontaneous (or induced) mutation rates increase according to the number of previous cell generations [114]. (2) For a cell to mutate, it needs to divide [115]. This basic observation is compulsory. Yet the widely agreed observation is that the number of stem cells decreases with ageing. Consequently, this leads to conceive that the probability of mutations should be lower in elderly people than in young people, although in the former, the total number of mutations can be higher due to the bioaccumulation process. (3) While it seems clear that ageing can be associated with physiological immunodeficiency and that, in general, immunodeficiency, be it innate or acquired, can favour virus-induced mutagenesis, there is no convincing experimental or clinical data suggesting that ageing per se can spur the initiation of cancers in elderly people. This means that, as much as ageing-related immunodeficiency may play a role in carcinogenesis due to a deficiency in the immunosurveillance system (role of K and NK cells), it should intervene in the promotion phase and not in the initiation phase. From these data, we conclude that ageing per se cannot be the exclusive risk factor, which contributes to initiate cancer, but rather, if we assume that many environmental factors are mutagenic, that cancer risk is clearly related to age, i.e. to the duration of exposure to these factors.

3. Environmental causing cancer agents

In order to justify the hypothesis according to which the growing incidence of cancers could actually be related to
environmental factors, we examine environmental carcinogens, in particular mutagens, and analyse their potential role in inducing cancers.

3.1. Viruses and other microorganisms

It is estimated that oncogenic viruses are involved worldwide in about 16% of neoplasia [116], with a range from less than 10% in high-income countries to 25% in Africa [117,118]. However, because in Western countries, there are some cancer types for which a viral origin is suspected, although not yet proved, it is likely that the figure of 5–10% is underestimated. Three groups of double-stranded DNA viruses and two groups of diploid RNA viruses have been shown to be associated with human cancers (Table 2). In Western developed countries, human papilloma virus (HPV), in particular HPV type 16 or 18 (HPV-16, HPV-18), and hepatitis B virus (HBV) are the most frequent oncogenic DNA viruses. These two viruses contribute differently to carcinogenesis: HPV-16 is directly mutagenic by inducing the viral genes E6 and E7 [119], while HBV is thought to be indirectly mutagenic by generating reactive oxygen species through chronic inflammation induction [120–122]. Epstein–Barr Virus (EBV) has been related to Hodgkin’s disease (HD) as well as to non-Hodgkin lymphoma (NHL) occurring in immunosuppressed patients [123,124]. In non-Western countries, in addition to the abovementioned cancers, Burkitt’s lymphoma and nasopharyngeal carcinoma have been shown to be caused by EBV, and Kaposi sarcoma (KS) to be associated with HIV and the Human herpes virus type 8 (HHV-8) [123,125–127].

RNA tumor viruses include the hepatitis C virus (HCV) and the unique retrovirus presently known to be oncogenic in humans, the human T-cell lymphotropic virus type 1 (HTLV-1). HTLV-1 is directly mutagenic, while HCV, as HBV, is thought to produce oxidative stress in infected cells and thus to act indirectly through chronic inflammation [128,129].

However, whatever their direct or indirect mechanisms of action, most of these DNA or RNA viruses are oncogenic, meaning that they can initiate carcinogenesis by inducing mutations. They must be therefore distinguished from other retro viruses such as the human immunodeficiency viruses (HIV) [130], which are not per se mutagenic, but which have been classified as carcinogenic by IARC, based on epidemiological data [126].

In fact, in addition to the abovementioned well established human virus-associated cancers, there are strong biological and epidemiological arguments for an infectious viral aetiology of other cancers [10]. Among microorganisms, oncogenic viruses are the most frequent and well established cancer causing agents. However, other microorganisms, including selected parasites such as Opisthorchis viverrini or Schistosoma haematobium and bacteria such as Helicobacter pylori may also be involved, acting as cofactors and/or carcinogens [2].

3.2. Radiations

Radiation-induced cancers are a stochastic late effect of ionizing or non-ionizing radiation. They include some leukaemia and lymphoma, thyroid cancers, skin cancers, some sarcomas and some lung and breast carcinomas [92].

Findings based on the study of lung cancer deaths associated with exposure to radon and improved understanding regarding the molecular basis of radon-induced cancers have provided support for incriminating low radon levels in the home environment as a cause of approximately 10% of lung cancers, and a higher proportion in underground miners [131,132]. Exposure to radon and radon decay products at home and/or at the workplace are the most widely found sources of exposure to ionizing radiation [133]. In contrast, contributions of human nuclear activities to radiation exposure of the general population, although generally estimated to be small and within the variations in background radioactivity, are nevertheless of serious concern [134,135]. Another source of radiation exposure corresponds to the use of X-rays in medical settings for diagnostic or therapeutic purposes. The examples are many but most noteworthy is the notion of period of exposure. For example, breast cancer risk is most increased among girls exposed to chest radiation around the age at puberty, at a time of intense breast development [Ronckers CM, Erdmann CA, Land CE. Radiation and breast cancer: a review of current evidence. Breast Cancer Res 2005;7:21–32.]. In addition to age and physiological state, radiation-induced cancers in humans depend on several variables, most of which are not possible to take into account fully for in traditional epidemiologic studies, such as issues of genetic susceptibility and for low dose chemicals low doses of ionizing radiation cannot be considered insignificant for risks of somatic and heritable mutations [136]. Among the other parameters to be considered

Table 2

<table>
<thead>
<tr>
<th>Virus family</th>
<th>Virus</th>
<th>Human tumors</th>
<th>Non-malignant disease</th>
<th>Experimental tumors in animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papovaviridae</td>
<td>Human papilloma virus</td>
<td>Cervical cancer, anogenital cancer, skin cancer</td>
<td>Warts</td>
<td></td>
</tr>
<tr>
<td>Herpesviridae</td>
<td>Epstein–Barr virus</td>
<td>Nasopharyngeal carcinoma, Burkitt’s lymphoma, Hodgkin’s lymphoma</td>
<td>Infectious mononucleosis, Lymphoma in primates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kaposi’s sarcoma-associated herpes virus</td>
<td>Kaposi’s sarcoma, primary effusion lymphoma</td>
<td>Multicentric, Castleman’s disease, Not known</td>
<td></td>
</tr>
<tr>
<td>Retroviridae</td>
<td>HTLV-1</td>
<td>Adult T-cell leukemia (ATL)</td>
<td>Tropical spastic paraparesis, ATL in rabbits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td>B-cell lymphoma, Kaposi’s sarcoma</td>
<td>AIDS</td>
<td></td>
</tr>
<tr>
<td>Hepadnaviridae</td>
<td>Hepatitis B virus</td>
<td>Liver cancer</td>
<td>Hepatitis, cirrhosis, Not known</td>
<td></td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>Hepatitis C virus</td>
<td>Liver cancer</td>
<td>Hepatitis, cirrhosis, Not known</td>
<td></td>
</tr>
</tbody>
</table>
are the synergistic interactions of radiation with other physical, chemical or biological carcinogens. Studies of cancer risks from nuclear power plant accidents are thus a challenge. Nevertheless, an increased incidence of the total malignancies after the Chernobyl radioactive fallout was reported in Sweden [137].

Ultraviolet (UV) rays, which have been rated as carcinogenic to humans by IARC [138]. Exposure to UV is a dose-dependent risk factor [139,140], which can cause skin cancers, mostly basal cell and squamous cell carcinoma [141–144]. It can be also involved in melanoma occurrence [138] and consequently, may be responsible for its current growing incidence.

Electromagnetic fields (EMF) of very low frequency (VLF) or extremely low frequency (ELF) have been the object of many scientific research efforts to answer the question whether or not they can induce cancers. It has been observed that pulsed EMF can be clastogenic by breaking DNA [145], but the mechanism whereby VLF or ELF could induce cancer is not clear. To date many studies correlating EMF to childhood acute leukemia have been reported [146,147]. Despite differences in study design and setting, the results are sufficiently consistent to indicate that an increased risk of leukemia does exist in children with high exposure [148–150]. Other epidemiological studies revealed that EMF and mostly ELF could be also associated with brain tumors [151–154] and breast carcinoma [92,153,154]. The most visible source of ELF EMF is power lines, in particular high voltage transmission lines, but other sources include transformers, electric train engines and more generally all types of electrical equipment. In a series of recent epidemiological studies, it has been shown that long-term cellular or cordless phone use is also a risk factor for brain tumors [157,158], whereas several previous studies showed negative results. Indeed, in a recent meta-analysis of all the available epidemiologic data, daily prolonged use of mobile phones associated with a long-term use for 10 years or more has been shown to give a consistent pattern of an increased risk of brain tumors including neuroma and glioma and the risk is highest for ipsilateral exposure [159].

3.3. Occupational cancers

Since the seminal report of Sir Percival Pott in 1775, cancers of the scrotum were the first recognized occupational chemically-induced cancer. Today, occupational cancers are reported to represent 2–10% of all cancers, but this percentage is probably underestimated and may be as high as 15–20% in men. In 1996, the Harvard Center for Cancer Prevention (HCCP) [313] classified 32 substances or industries as carcinogenic in humans [160]. Recently, 28 agents have been considered as definite occupational carcinogens in human, 27 as probable occupational carcinogens and 113 as possible occupational carcinogens [161,162]. Doll and Peto (1981) had listed only 16 in 1981 [51]. In Europe, there could be 32 million people exposed to hazardous carcinogenic chemicals at work [163]. Among carcinogenic substances, asbestos is a classical example. There is no doubt that asbestos is carcinogenic and induces occupational cancers, including mesothelioma and approximately 10% of lung cancer [147,164,165]. Likewise, wood-dust-related cancers, although their occurrence is mostly limited to joiners or cabinet makers is limited, are also occupational cancers, insufficiently declared (ethmoid cancers) or even not yet declared (sinus cancers) [166,167]. Solvents, paints, dyes, gasoline and other petroleum products can also cause occupational cancers. After the leukemogenic effect of benzene was first recognized [168,169], the mutagenic effect of other solvents was established. For example, trichloroethylene has been reported to be strongly associated with kidney, liver, esophageal cancers and non-Hodgkin’s lymphoma [170–175] and perchloroethylene with esophageal cancers [176,177]. Likewise, dye products or byproducts of aromatic amines and/or aminophenol groups are strongly associated with bladder cancer [179]. Moreover mineral oils and lubricants have been associated with some types of cancers, including larynx, skin and bladder cancers [179–184]. Phthalates are widely used since the last world war, due to their plasticizing and emulsifying properties. For this reason, they are added to polyvinyl chloride (PVC) in particular in common medical devices and cosmetics. Di(2-ethylhexyl)phthalate (DEHP) and butyl-benzyl-phthalate have been suspected to be carcinogenic [185]. Toxicological studies in rodents indicate that DEHP exposure can cause liver cancer [186] and pancreatic tumors [187]. Three studies in humans revealed an elevated pancreatic cancer risk in workers in flexible PVC processing [188–190]. IARC initially classified DEHP as a 2B possible carcinogen to humans, but subsequently downgraded it to a non-classifiable grade 3 molecule [191]. However, none of the studies indicating an elevated risk of pancreatic cancers in humans exposed to DEHP were considered [192]. Thus the IARC evaluation on DEHP, because it omitted critical available information from relevant animal and human studies, was criticized by many scientists to such an extent that they asked IARC to schedule a new, thorough and unbiased DEHP evaluation. In addition, vinyl chloride monomer, but not PVC, is mutagenic and thus can cause liver angiosarcoma and hepatocellular carcinoma (HCC) [193].

A major concern is the risk of childhood cancers following either parental or child exposure to occupational pollutants. Several studies, evaluating the effect of parental exposure to solvents, paints, and gasoline exhaust, showed an increased risk of leukemia and brain tumors in children [194–198]. However, the global impact of these different types of mutagenic chemicals or substances in the general population is still under investigation and remains to be quantified.

3.4. Outdoor air pollution

Polycyclic aromatic hydrocarbons (PAH) resulting from the combustion of organic substances are mutagens [181]. They are found in tobacco smoke as well as in any combustion product including many sources of pollution such as factory smoke, waste incinerator emission and vehicle exhaust. They can adhere to fine carbon particles (PM 2.5) suspended in the air and thus penetrate the organism more extensively because the particles accumulate near the ground at the level we breathe. In adults, long-term exposure to particles and so
to PAH, i.e. in the air of polluted cities, increases the risk of death due to lung cancer by up to 8%, after controlling for tobacco smoking [199–201]. In 2002, the American Cancer Society published the results of a study on 500,000 people residing in American cities: the higher the concentration of fine particles in the air, the higher the number of deaths due to lung cancer. This risk is significantly higher for the more polluted cities than for the less polluted ones, and smoking potentiates that effect [200]. Moreover, in a recent European study, the proportion of lung cancers attributable to traffic-related air pollution and environmental tobacco smoke (ETS) in never- and ex-smokers was estimated to be 5–7% and 16–24%, respectively [202]. In addition to PAH and fine and ultrafine carbon particles the air pollutant nitrogen dioxide (NO2) may also be involved. NO2 is a marker of a mixture of particles and gases related to traffic, power plants and/or waste incinerator emission. Experimental studies have shown that NO2 can contribute to lung cancer induction [203,204] and facilitate metastatic dissemination [205] and that after NO2 combines with benzo[a]pyrene, the resulting product, i.e. nitrobenzo[a]pyrene, is characterized by an increased mutagenicity compared to benzo[a]pyrene alone [206]. In the above described European epidemiological study, it was observed that a higher exposure to NO2 increases the risk of lung cancer in non-smokers [202]. Because they have a more rapid rate of respiration and so inhale more pollutants per kilogram of body weight than adults, children are more susceptible to air pollution. Traffic exhaust is a major cause of children’s exposure to air pollutants [181] and several authors in the US as well as in Europe found a positive correlation between local traffic density at the time of diagnosis and childhood leukemias with an estimated relative risk between 1.6 and 4.7 [207–210].

3.5. Indoor air pollution

Indoor air pollution is a growing scientific concern because indoor air can lead to a concentration of many carcinogenic pollutants. In addition to carbon particles and PAH, indoor air can accumulate ETS as well as chemicals such as biocides and formaldehyde in addition to volatile organic compounds (VOC) such as benzene and 1,3 butadiene, which have been rated as carcinogens by IARC [211]. The risk of lung cancer due to ETS exposure is slightly higher at work than at home and higher for ex-smokers than for never smokers [202]. Since children are the most affected by chronic household exposure, they may be at a higher risk of cancer. Particularly of concern is the association between parental and/or childhood exposure and the risk of childhood cancers [212] and cancers in adulthood [202]. There is an increased relative risk of leukemia and lymphoma caused by indoor VOC [213–215] as well as by the indoor use of insecticides [216–218].

3.6. Biocides and pesticides

Over the last decades, several hundreds of pesticides have been marketed for intensive farming or domestic use (biocides). Many of them especially those belonging the organochlorines, carbamates and carbinals groups are rated as probable or possible carcinogens, according to the US EPA and the IARC classification [219] while several are recognized as carcinogens in humans. Most of them having a molecular structure close to estrogens or androgens are called endocrine disruptors. They may act as promoters, while others can in addition be mutagenic. Moreover many of them are also strong immunosuppressors, meaning that they can act also as promoters through immunosuppression [220,221]. In children, several epidemiological studies revealed an increased relative risk of cancers associated with parental exposure to pesticides, be it occupational or non-occupational [222,223]. The exposure occurred prior to and during pregnancy as well as post-natally. Paternal exposure to pesticides is associated with an excess relative risk of leukemia [224], and of central nervous system tumors [225,226] as well as of Wilm’s tumors [227]. Moreover a positive association has been found in several studies testing the direct exposure of children to pesticides [218,222,223,228]. Collectively, these studies revealed an overall increase in the relative risk of leukemia, NHL, brain tumors, Wilm’s tumors, Ewing’s sarcoma and germ cell tumors associated with parental or child exposures to pesticides. By contrast, in adults, epidemiological studies have provided conflicting results. A positive link between pesticides and breast or prostate cancers has been put forward in some studies [229–232], whereas in other studies it cannot be confirmed [65,233–235]. However, a strong association between pesticides and the relative risk of sarcoma [236,237], Hodgkin and NHL [238–241] has been found for 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), chlorophenols and phenoxycarbinoids. Likewise an increased risk of adult leukemia has been shown for carbon disulfide, phosphine (such as PH3) and methyl bromide [237]. Indeed, due to their CMR effects, organochlorine pesticides are today almost universally banned in most industrialized countries. The danger of pesticides lies in the fact that as persistent organic pollutants (POPs), they can persist over long periods in the environment and contaminate drinking water and food [242]. Indeed, pesticides can contaminate the body not only through ingestion, but also through air inhalation and skin contact, accumulate in adipose tissue [243–245], more specifically in fatty breast tissue [246,247], pass through the placenta [248] and accumulate in the milk of nursing mothers [249]. This led to the conclusion that children are at risk during three periods: in utero during pregnancy, during breast feeding and in the course of childhood, by inhaling biocides at home, having contamination on their skin (in particular on their hands) or by ingesting contaminated food [218,250]. During recent years there has been an increasing incidence of male developmental reproductive disorders. These diseases have been grouped together in the testicular dysgenesis syndrome and include testicular cancer, cryptorchidism, hypospadias and low sperm count [251]. Exposure to endocrine disrupting chemicals during the fetal period has been postulated to be a risk factor. In a case-control study concentrations of certain persistent organic pollutants such as polychlorinated biphenyls were higher in the mothers of young men with testicular cancer compared with the mothers of controls [252].
3.7. Dioxins and other organochlorines

Organochlorines are CMR molecules, which result either from the combustion of organic substances in contact with chlorine or from industrial chemical synthesis. Examples are dioxins, which may be produced from the incineration of halogenated plastics (such as PVC), pesticides such as hexachlorobenzene (HCB) and polychlorinated biphenyls (PCB). On the basis of a myriad of in vitro and animal studies, it has been clearly shown that these chemicals are endocrine disruptors, may interfere with the developmental process in utero and can cause cancer through a promoting or cocarcinogenic effect [253–256]. Moreover, some of them, such as PCB and dioxins, have been shown in addition to be mutagenic [254,257]. In 1979, following the Seveso accident, IARC rated 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a 2B possible human carcinogen [258], but this categorisation was upgraded to a recognized group 1 carcinogen in humans in 1997 [259]. Since then, some studies have shown an increased relative risk of sarcoma and lymphoma in the vicinity of incinerators and related this increased risk to dioxin emission [260–262]. Although the carcinogenic mechanism of dioxins is not clear, an association between chronic exposure and an increased incidence of several cancer types has been put forward [259] indicating the important and extensive spectrum of their carcinogenic effect. Other suspected carcinogenic organochlorines deal with the problem of long-term exposure to chlorinated water which has been shown to be associated with an increased risk of cancer including bladder cancer [263–268], colorectal cancer [269,270] and adult leukemia [271]. Chlorine is not itself carcinogenic but can combine with organic matter in drinking water and form chlorination disinfection byproducts including trihalomethanes and haloacetic acids which have been demonstrated to be mutagenic in vitro and in vivo [272] and carcinogenic in animal models [273]. Finally, the danger of organochlorines lies in the fact that, as pesticides, they are POP and accumulate in the body’s adipose tissue from which they are released.

3.8. Food contaminants and food additives

Nitrates, pesticides and dioxins can contaminate drinking water and food. Nitrates are used in intensive farming. They are not intrinsically carcinogenic, but can be endogenously transformed into nitrites by the digestive bacterial microflora, which in turn can be further transformed into N-nitroso compounds (NOC), i.e. into alkyl-nitrosamines and nitrosamides through nitrosation [274,275]. These are highly mutagenic molecules. Secondary or tertiary amines and amides are found as common dietary contaminants [275]. Long-term exposure to food additives, including nitrite preservatives and artificial azo dyes, may be also involved in chemically-induced carcinogenesis, due to their mutagenic properties [276–278]. In addition, bisphenol A, a xenoestrogen used in plastic food containers, because it can migrate in food and be repeatedly ingested, has been recently suspected to be carcinogenic in humans on the basis of results obtained from animal studies aiming at reproducing breast [279] and prostate cancer [280,281]. This led to the hypothesis that in association with diet and nutrition lifestyle-related factors, chronic exposure to food contaminants and food additives might be involved in carcinogenesis more frequently than it is usually appreciated. Since NOC are powerful transplacental neurocarcinogens [282], they may be involved in the recent increase of childhood brain tumors [283]. In adults, a few epidemiologic studies have found an excess consumption of nitrates to be associated with an elevated risk for gastric and nasopharyngeal cancers [178]. Moreover, an increased risk of NHL [284] and of colon cancer [285] has been put forward in association with drinking water with the nitrates’ concentration over the regulatory level. However, because the pollution by nitrates impacts the general population, and because the transformation of nitrates into mutagenic NOC depends on many factors, including diet and microflora modifications, their carcinogenic role is difficult to clearly assess through epidemiological studies [275].

3.9. Metals and metalloids

Several metals and metalloids have been rated as certain or probable carcinogens by the IARC [286]. Inhalation of arsenic oxides can cause lung cancer, but if swallowed, cancer can develop in the bladder, kidney, liver and lung [287]. Thus exposure to arsenic oxides has been reported to be associated with a very large spectrum of common cancer types. Aside from arsenic oxides’ exposure, lung cancer has also been reported to be associated with exposure to many metals, including lead, hexavalent chromium and nickel [288]. Furthermore, exposure to hexavalent chromium or nickel has been found to be associated with nasopharyngeal carcinoma, exposure to lead or mercury to brain tumors, exposure to lead or cadmium to kidney cancer and exposure to cadmium to prostate cancer [289–294]. The mechanisms of the action of metals and metalloids are not clear yet. They could act as cocarcinogens by activating procarcinogens in the liver [178,289] or by increasing the promoting effect of estrogens [295]. They could also act by replacing the natural enzyme-associated metal, thus inactivating the metabolic pathway of key enzymes. Carcinogenic metals and metalloids, such as arsenic, cadmium and nickel, and putative carcinogens including cobalt and lead can inhibit zinc finger containing DNA repair proteins. Damage of zinc finger in DNA repair proteins can therefore be regarded as a novel mechanism in carcinogenesis [296]. Moreover, some metals and metalloids may also be mutagenic through other mechanisms, since many of them can interact with DNA.

3.10. Medicines and products of personal care such as cosmetics

The best acknowledged class of pharmaceutical drugs classified as carcinogens corresponds to hormonal products, which include oral contraceptives and hormone replacement therapy [297,298], as well as anti-estrogens such as tamoxifen [297]. Clearly, oral contraceptives, in particular when taken before the first pregnancy as well as hormone replacement therapy,
because they act as promoters, have been demonstrated to be associated with a small increased risk of breast cancer, especially when they are taken during a long period [298,299]. Consequently, a serious medical risk—benefit evaluation has to be carried out by women, be they in search of contraception, management of menopausal symptoms by hormonal substitutive treatments or prevention of breast cancer by tamoxifen. Other carcinogenic medicines include many anticancer chemotherapeutic agents which can cause the late occurrence of secondary cancers in apparently cured cancer patients due to their mutagenic properties [300–302]. However, the ratio between benefit and toxicity is so high that the use of chemotherapeutic agents in oncology is not questioned although efforts are made to adapt the dose or look for replacement products. By contrast the question is more difficult for drugs given to healthy persons. Cosmetics which include some recognized carcinogenic molecules such as formaldehyde or hormonal products or some putative ones, such as phthalates or parabens have been recently the object of many concerns. Parabens in underarm deodorants have been suspected to be an etiological factor of breast cancer [303,304] but this hypothesis is not validated yet and, to our knowledge, no formal study has been designed and carried out to clarify this problem. By contrast, it has been found that permanent hair-dyes, containing aromatic amines, may increase the relative risk of bladder cancer by 3.3-fold among regular users relative to non-users [305], although the estimate is only at 1.2 to 1.5 in a recent meta-analysis [306]. In addition, it has been shown that permanent hair-dyes carries a relative risk of adult acute leukemia of 2.4 in women for a use of up to six times per year for more than 15 years [307]. Although these data have been recently challenged [308], they have been confirmed in a systematic review of the scientific literature published since 1992: positive associations between personal hair-dye use and bladder cancer, acute leukemia, lymphoma and myeloma have been clearly observed in well-designed studies [309].

4. Conclusion

The industrial revolution over the second half of the last century and its consequences in domains such as energy, transport, agriculture, food and health led to synthesize, produce and introduce into the environment, millions of man-made chemicals or substances. As a result, according to the European commission, about 100,000 chemicals have been so far marketed, since the last world war, without sufficient toxicological control. Such products can act as persistent toxic pollutants and contaminate air, soil, water and food. Many of them are CMR molecules [162] and therefore can act as mutagens, promoters or both or be cocarcinogenic [10], meaning that they can contribute to the genesis of cancers and therefore may account for their currently growing incidence [5,310].

Finally, from this overview, although there are still some persisting areas of uncertainty, it clearly appears that due to their mutagenic and/or promoting properties or to their cocarcinogenic effects, many exogenous environmental factors, including viruses, radiation and xenochemicals can contribute to cause a variety of cancers.

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Dossier : Cancer : Influence of environment

The cancer incidence temporality index: An index to show temporal changes in the age of onset of overall and specific cancer (England and Wales, 1971–1999)

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Received 13 April 2007; accepted 2 May 2007
Available online 6 June 2007

Abstract

The theory that increasing cancer incidence rates in developed countries are primarily the consequence of an expanding ageing population and improved diagnostic testing is widely held. In the United Kingdom the proportion of people aged 50 and over has increased by 45% since 1951 and this proportion is set to increase by a further 36% by the year 2031, so the United Kingdom does indeed have an expanding ageing population. However, the increase in cancer incidence affects people across the whole age spectrum. To test the hypothesis that the age of onset of cancer (overall and specific) in England and Wales is decreasing over time we have developed The Cancer Incidence Temporality Index (CITI), which gives a crude measurement of the portion of the population, in which cancer incidence is rising fastest over time: \[ I = \frac{\sum O_a / \sum E_a}{\sum O_b / \sum E_b}, \]
where \( I \) is the CITI value, \( O \) is the observed number of cases and \( E \) is the expected number of cases; ‘a’ and ‘b’ refer to separate summation ranges for younger and older age groups. Population data and cancer incidence data in England and Wales, 1971–1999 were obtained from the UK Office for National Statistics. The trends in CITI values have been shown graphically for cancer overall and for specific tumour sites. The impact of diagnostic testing is also addressed. The results of this study suggest that the average age of onset of prostate, breast and cervical cancer is temporally decreasing. The study also suggests that for cancer overall the trend for the age of onset of cancer in males has stabilised since 1990 and has started to reverse in females from 1995 despite the expanding ageing population. A similar trend is observed for leukaemias. The CITI analysis for colon cancer shows that the age of onset in both males and females is increasing over time. The trend for ovarian cancer is similar to that for colon cancer. The CITI analysis for NHL in males is similar to that for colon cancer, however, in females the trend stabilised after 1990. The CITI may aid prediction of changes in the age of onset of cancer and thus aid targeted aetiological research. In addition, we suggest the need for a mathematical model, which may measure the changes in the age of onset of cancer in units of time.

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Keywords: Age of onset; Cancer; Ageing

1. Introduction

A question that is consistently asked by clinicians, epidemiologists and scientists is ‘why has there been a long-term upward trend in cancer incidence rates in developed countries?’. It is becoming apparent that this is also progressively more the case in developing countries. In the European Union, there are around 1.9 million new diagnoses of cancer and 1 million deaths from malignant disease per annum. In the last 5 years, an estimated 3 million people are alive in the European Union who received a diagnosis of cancer [1]. The
most widely postulated theory is that increased cancer incidence is primarily due to the expanding ageing population [2–7].

The United Kingdom population estimate for mid 2004 suggests that the UK has a population approaching 60 million people (59.8 million). The United Kingdom does indeed have an expanding ageing population. In 2003 there were 20 million people aged 50 and over; this is an increase of 45% from 13. million since 1951. This number may increase by a further 36% to 27.2 million by 2031. Since 1971 the proportion of people over 65 has increased from 13% to 16%. If people over the age of 65 are considered, the proportion of people aged 85 and over since 1971 increased from 7% to 12%. It is thought that population ageing will continue during the first half of this century due to the large number of people born after the Second World War and during the 1960s baby boom becoming older [8].

The theory that increasing cancer incidence is primarily a consequence of an expanding ageing population is based on the hypothesis that people are living longer and therefore have a greater chance of accumulating enough mutations needed for malignant transformation of cells, according to the multi-stage theory of carcinogenesis postulated by Armitage and Doll [9]. Accumulation of six or seven mutations are needed for malignant transformation of cells, therefore, greater longevity suggests more mutations hence more cancer. In addition, it is also postulated that cancer screening and improved diagnostic techniques, which can detect small, latent tumours that may never develop into symptomatic cancers lead to overdiagnosis and consequently increased incidence [2,10,11].

Cancer Research UK [2] state, ‘If current age specific cancer incidence rates remain the same, by 2025 there will be an additional 100,000 cases of cancer diagnosed each year as a result of the ageing population.’ A report carried out by the Department of Epidemiology and Surveillance Research [12] stated, ‘Despite reductions in age-adjusted rates of cancer death, the total number of recorded cancer deaths in the United States continues to increase, due to an aging and expanding population.’

It is apparent from age-specific cancer incidence figures that the majority of cancers in the United Kingdom and other developed countries occur in elderly people. Sixty-four percent of malignant disease in the United Kingdom is observed in the over 65s (see Fig. 1) [2]. However, although cancer is more prevalent in older age groups, this is not inconsistent with living life in an environment which has become rich in man-made carcinogenic influences.

Around 1% of cancer cases in the United Kingdom occur in children, in 2002 there were 1500 cases recorded (age 0–14). In adolescents and young adults (age 15–24), 1700 cases were recorded in 2002 [2]. This figure does not include 4000 cases of carcinoma in situ of the cervix in young women aged 15–24. According to Cancer Research UK [2], the vast majority of these preinvasive lesions are detected through smear tests. For Europe as a whole around 1% of cancers occur in people aged under 20, the largest increases in this age group are found in children under 3 and adolescents aged 14–19 [13]. Although childhood cancer could be perceived to be a small fraction of total cancer incidence, the rates have consistently increased year on year.

In the USA, the childhood cancer incidence rate during the past 30 years has increased by 1% per annum [14]. Steliarova-Foucher et al. [13] assessed changes in childhood cancer incidence rates since the 1970s in Europe and concluded that the rates increased and accelerated. The rate changes are comparable to the USA. The overall incidence rate in the United Kingdom for childhood and adolescent cancers and cancers in young adults increases by 1.5% per annum [15–17].

Ageing cannot be considered as a unique factor in cancer aetiology because the increased incidence in malignant disease is observed across the whole age spectrum, [18,19]. To test the hypothesis that the age of onset of cancer (overall and specific tumour sites) in England and Wales is temporally decreasing, we have developed the Cancer Incidence Temporality Index (CITI), which gives a crude measurement of the portion of the population, in which cancer incidence is rising faster over time.

2. Method

Cancer incidence data in the form of a Microsoft Excel file was obtained from the UK Office for National Statistics, courtesy of Dr Steve Rowan. The data consisted of cancer registrations, crude incidence rate/105 population, age standardised incidence rate/105 population (standardised to European population), for England and Wales, during 1971–1999, in males and females. The data were provided by sex and in 5-year age groups and were obtained for the following tumour sites, hormonally regulated: prostate (C61),1 testes (C62), breast (C50), uterus (C54), cervix (C53) and ovary (C56–57);

1 Code denotes an established method of classifying tumours derived from the international classification of disease.
non-hormonally regulated: lung (C33–34), pancreas (C25), colon (C18), colorectal (C18–21). In addition, data were obtained for non-Hodgkin’s lymphoma (82–85), leukaemias (C91–95) and all malignancies (C00–97 × C44). Population data were also provided for the years 1971–1999 inclusive for England and Wales by sex and 5-year age group. A separate file was used for each specific cancer site studied.

To facilitate determination of the CITI, data were entered into a separate workbook for each tumour site listed above using the Microsoft Excel spreadsheet package. Data was entered for the year 1971 under the column headings: age group, population, cases and ratio. Data was then entered for the years 1972–1999 under the column headings: population, expected, expected cut (ratio), observed and observed/expected (see Figs. 2–4).

2.1. Determination of the Cancer Incidence Temporality Index (CITI)

The CITI is based on the year 1971 = 1; complete cancer incidence and population data were only available from 1971. To calculate the CITI value, an appropriate age group was chosen as a cut off point. To establish the appropriate cut off point the age group in 1971 was chosen where the ratio of cases above (a) and below (b) was closest or equal to 1. Expected numbers of cases for each year were calculated by multiplying the population data for each year by the crude rate for 1971/105.

The CITI value for each year and age group was calculated using the following formula:

\[ I = \frac{\sum O_a}{\sum O_b/\sum E_b} \]

where \( I \) is the index value, \( O \) is the observed number of cases and \( E \) is the expected number of cases. The summations are for 5-year age groups in younger age span ‘a’ and in older span ‘b’. For example,

\[ \sum E_a = \text{rate}_{0-4}(\text{pop})_{0-4} + \text{rate}_{5-9}(\text{pop})_{5-9} \]

\[ + \text{rate}_{10-14}(\text{pop})_{10-14} \]

where \( \kappa \) is age groups up to the cut off point.

\[ \sum E_a = R_k(P_k) \text{ or } (R \cdot P)_k \]

A CITI value >1 for a particular year indicates that the incidence rate of a specific cancer in the population younger than the cut off point is rising faster than the incidence rate in the population older than the cut off point. An example of index analysis showing first 3 years of calculations for prostate cancer is shown in Fig. 3.

3. Results

3.1. All malignancies (ICD10: C00–97)

The results of the CITI analysis for all malignancies for males (cut off point 60–64) show that the CITI value falls below 1 in 1972 (CITI value 0.99) and continues to decrease through to 1989 to a minimum CITI value of 0.79. The CITI values then stabilise to around 0.83–0.82 from 1990 to 1999. For females the CITI analysis for all malignancies (cut of point 65–69) shows that the CITI values fall below 1 in 1973 (0.98) and continue to fall until 1989 to a minimum CITI value of 0.84. The CITI values then stabilise at around 0.86 until 1995 where the CITI value rise to a CITI value of 0.88 in 1989 (see Fig. 5).

3.2. Specific tumour sites

3.2.1. Prostate cancer (ICD10, C61)

The CITI analysis for prostate cancer (cut off point 70–74) resulted in a CITI value trend >1 from 1972, (CITI value 1.07)
which is the minimum value. The CITI values continue to rise over time to 1990 to a CITI value of 1.12. From 1990 a steep increase in CITI value from 1.12 in 1991 to a maximum CITI value of 1.64 in 1999 (see Fig. 6).

3.2.2. Breast cancer (ICD10: C50)

The CITI analysis for breast cancer (cut off point 60–64) shows that the CITI value initially rises above 1 from 1972 to 1974 (index value 1.07–1.02). The value then falls below 1 in 1975 (0.98) and continues to decrease over time until 1988 to a minimum CITI value of 0.92. The trend in the CITI value reverses from 1989 to 1992 (CITI values 0.94–1.02) when the CITI value rises >1 through to 1999 to a maximum CITI value of 1.04 (see Fig. 6).

3.2.3. Colon cancer (ICD10: C18)

The CITI analysis for colon cancer in males (cut off point 65–69) shows a continuing decrease in CITI value <1 from 1973 (CITI value 0.94) through to a minimum CITI value in 1994 of 0.82 (CITI value at 1999 of 0.85). The CITI analysis for females (cut off point 70–74) shows a similar trend to that of males. The CITI values fall below 1 in 1972 (0.98) to a minimum CITI value in 1997 of 0.83 (CITI value in 1999 of 0.87) (see Fig. 6).

3.2.4. Cervix uteri (ICD10: C53)

The CITI analysis for cervical cancer (cut off point 55–59) shows an initial fall in CITI value below 1 in 1972 (0.86)
which continues to fall to a minimum CITI value of 0.78 in 1975. The CITI values begin to rise and reach a CITI value >1 in 1983 (1.01) and continue to rise to a maximum CITI value in 1989 of 1.25 (CITI value in 1999 of 1.22) (see Fig. 6).

3.2.5. Leukaemias (ICD10: C91–95)

The CITI analysis for leukaemias for males (cut off point 60–64) shows a fall in CITI value below 1 in 1983 (1.01) and continue to rise to a maximum CITI value in 1989 of 1.25 (CITI value in 1999 of 1.22) (see Fig. 6).

3.2.6. Ovarian cancer (ICD10: 56–57)

The CITI analysis for ovarian cancer (cut off point 60–64) shows a fall in CITI value below 1 in 1972 (0.96) and continues to fall to a minimum CITI in 1988 of 0.67. The trend in CITI values then stabilises over time to a final CITI value in 1999 of 0.74. The CITI analysis for females (cut off point 65–69) shows a very similar trend to that of males; CITI values falling to a minimum in 1988 of 0.80. However, following stabilisation of the trend from 1991–1995, the trend in CITI values starts to increase to a final CITI value of 0.88 in 1999 (see Fig. 7). Of course, ‘all leukaemias’ is dominated by chronic lymphatic leukaemia in the older age groups and the CITI would not inform us about changes in acute lymphatic leukemia in young persons.

3.2.7. Non-Hodgkin’s lymphoma (NHL), (ICD10: C82–85, C91.4, C96)

The CITI analysis for NHL for males (cut off point 60–64) shows a continuing fall in CITI values below 1 from 1972 falling to a minimum CITI value in 1999 of 0.63. The CITI analysis for NHL in females (cut off point 65–69) shows a similar trend to that for males. The CITI values fall below 1 in 1972 and continue to fall to a minimum CITI value in 1989 of 0.69. However, in contrast to males the CITI values then begin to stabilise to a final value in 1999 of 0.80 (see Fig. 7).

4. Discussion

The increase in cancer incidence in the developed world is generally thought to be primarily a consequence of an expanding aging population. To test the hypothesis that the age of onset of cancer is decreasing over time, we developed the CITI to measure temporal changes in the age of onset in England and Wales, 1971–1999.

Increasing cancer incidence in the developed world affects the whole age spectrum and this study suggests that the age of onset for prostate and breast cancers, and cancers of the cervix uteri is decreasing over time. The results for all malignancies suggest that the age of onset increased over time, however, in the last 5 years of the study this trend stabilised in males, and has stabilised then reversed in females suggesting that the age of onset may be starting to decrease, despite the expansion of the ageing population and despite the proportion of the female population aged 65 being greater than the male portion.

The results for leukaemias show similar trends to that for all malignancies for both males and females. The trend in CITI values for NHL suggests that the age of onset has
continued to increase over time for males. The trend for females is similar until 1989–1999 when the trend stabilised, i.e., the age of onset remains fairly stable. The results for colon cancer in males and females suggest that the age of onset is increasing over time. There is a similar trend observed for ovarian cancer.

Some researchers [2,10,11] suggest that in addition to the expanding ageing population increased cancer incidence is also a consequence of screening and improved diagnostic techniques, for example prostate specific antigen (PSA) testing for prostate cancer [20], cervical smear tests to diagnose cervical cancer or precancerous lesions [21] and mammography used for breast cancer screening [22]. It is thought that these techniques find latent tumours that will never progress, or progress very slowly into symptomatic malignacies but these tumours are reported to cancer registries and may be responsible for the increased incidence rate and possibly to over diagnosis [23,24]. This is known as ‘length–time’ bias, which occurs because slow-growing, less aggressive tumours by definition have a longer asymptomatic period and are therefore more likely to be detected by screening. A study by Stenman et al. [10] suggests that PSA testing can detect a latent tumour on average 5–10 years before becoming clinically significant (‘harvesting effect’) and 17 years on average before death of the patient would be caused.

The introduction of PSA measurement could explain the results for prostate cancer in the CITI study. These show a sharp increase in CITI values after 1992, the time PSA testing was introduced to the United Kingdom. Although in the United Kingdom there is no routine screening program for asymptomatic males thought to be in the age range at risk for prostate cancer, there has been an increase in PSA testing since 1992 when the test became widespread [23]. For example, in the East Anglia region of the United Kingdom between 1991 and 2000, a 6% excess in prostate cancer registrations relative to expectations based on pre 1991 trends was found. This excess was coincidental with increased PSA testing [25]. PSA testing in the United Kingdom in men over the age of 40 with no previous diagnosis of prostate cancer has increased from 1.4% in 1994 to 3.5% in 1999 [26].

Improved diagnosis did not seem to be an important factor according to Post et al. [27], the authors of a study examining prostate cancer epidemiology in the same area of the United Kingdom as [23,25]. Post et al. [27] studied prostate cancer incidence and mortality rates in men aged <60 prior to the introduction of PSA testing from 1971 to 1990, when transurethral resection of the prostate (TURP) was used for treatment of benign prostate hyperplasia (BPH) and sometimes resulted in the incidental detection of subclinical prostate cancer in around 10% of cases, prior to the introduction of PSA testing. The authors thought that because BPH in men aged <60 is less prevalent than men aged >70 and therefore TURP is around seven times less likely, the increase in incidence in younger men may not be caused by higher detection rates. The study found no improvement in prognosis in the period in the era preceding PSA testing in men aged 40–59. They concluded that improved diagnosis testing did not seem to be an important factor because more subclinical non-aggressive tumours would have been found producing an improved survival rate. The authors also described the increase in prostate cancer incidence as striking.

In addition, the prostate cancer incidence rate in England and Wales, 1971–1993 (prior to PSA testing) more than doubled. The annual number of new cases of prostate cancer registered increased by 179% from 6174 to 17,210. Directly ASR increased by 104% from 29 to 59 per 100,000. The number of deaths from prostate cancer increased by 113% between 1971 and 1998, from 4027 to 8570 [28].

While some of the increased incidence may in part be due to the impact of screening techniques such as PSA testing. Is there any evidence of potential environmental causes of decreasing age of onset of prostate cancer? A retrospective study on males with biopsy-diagnosed carcinoma of the prostate in the USA by Potti et al. [29] found that the prostate cancer in young patients (<50) was associated with exposure to pesticides (>2300 h). Another interesting finding was that the median period of exposure for the pesticide-exposed patients was 11.3 months compared to a mean survival of non-exposed patients, which was 20.1 months.

In the case of breast cancer diagnosis, screening in the UK started in 1990 and is carried out by the NHS Breast Cancer Screening Program. The increase in CITI value above 1 seems to coincide with this year. Women between the age of 50–69 are invited to a screening every 3 years by an X-ray mammogram [30]. The latest research suggests that the screening programme has saved 1440 lives each year in England ([31]. Women under 50 are not offered routine screening because it is thought that mammography is not effective enough in premenopausal breast tissue because it is of a higher density than post-menopausal breast tissue and because breast cancer is more common in post-menopausal women [30]. The CITI analysis for breast cancer suggests that the average age of onset of breast cancer is decreasing thus indicating that premenopausal breast cancer may become more common. An interim study by the Cancer Screening Evaluation Unit of the Institute of Cancer Research to evaluate the effect of screening women from the age of 40 has reported that a reduction of breast cancer mortality may be observed.

Undoubtedly, diagnostic and screening techniques will contribute to the increased incidence rates, however the impact may not be as much as some researchers suggest. Norway routinely collected cancer incidence data for a long time before diagnostic testing was introduced for prostate and breast cancer; prior to the introduction of these tests, prostate cancer cases had increased by around 100%, breast cancer cases increased by almost 80% [32]. Similarly, in England and Wales prior to PSA testing, prostate cancer incidence during the period 1971–1993 increased by 179%. In addition, incidence has increased in cancers, which currently do not have diagnostic testing, for example testicular cancer, NHL and childhood cancers. A recent study by Raaschou-Nielsen et al. [33] suggests that the increasing rate of central nervous system tumours in children has truly increased and is not a consequence of improved diagnostic techniques.
Women in developed countries are delaying having children mainly due to socioeconomic reasons and evidence suggests that this may be influencing, to some extent, incidence rates. It is widely acknowledged that multiparity reduces the risk of breast cancer and null parity and delayed parity results in an increased risk of breast cancer [34–38]. In the United Kingdom, it is thought for each year that parity is delayed; the relative risk of breast cancer may increase by 3%. Therefore, a woman who has her first baby at age 28 would have a 3% lower risk of breast cancer than a woman who had her first baby at age 29 [2]. A study by Lee et al. [34] found an increased risk with advancing maternal age: women giving birth for the first time aged 41 had a 3.7% relative risk compared with women giving birth at age 23. It has also been postulated that age at last birth may be a factor for increased breast cancer risk [37,38]. However, the results from a study by Lambe et al. [36] contradict this theory. Breast feeding has been shown to reduce the risk of breast cancer by 4.3% for each year of breast feeding [2,35].

The CITI analysis in this study is a crude measurement of temporal changes in the age of onset of malignant disease in England and Wales. The limitation of the CITI is that the size of any temporal change cannot be measured in units of time. A further limitation of this study is that statistical significance of CITI values differing from 1 was not tested for. We considered finding confidence intervals for CITI values at three time points. However, it was thought a test for statistical significance would not be needed at this stage of the study because of the complexity of such a test and because the CITI in this form is a crude measurement of changes in the age of onset of cancer more accurately. The model may then be used to predict future changes in the age of onset and possibly to aid future direction of aetiological studies. A second point that needs to be made is that the CITI and its trends will be dependent upon the age cut off point. We chose to balance the older and younger ages, so that in 1971 the CITI value was unity. However, it may be argued that for some cancers, a lower age cut off point would be more valuable in highlighting variation in ages of onset. There is no a priori reason why the CITI should be made equal to unity: this was just a choice made to examine the properties of the parameter. For breast cancer, for example, choice of age 45 as a cut off point would highlight increases in the disease in young women below the age of 44.

The increasing cancer incidence rates in developed countries are suggested to be primarily a consequence of an ageing population. The results of this study suggest that the age of onset of prostate, breast and cervical cancers are temporally decreasing. The study also suggests that for cancer overall the trend for the age of onset of cancer in males has stabilised since 1996 and has started to reverse in females despite the expanding ageing population. Therefore we may conclude that the ageing of the population is not apparently the main factor driving the increased cancer rates in the England and Wales.

Acknowledgements

The authors gratefully acknowledge the assistance Dr Steve Rowan. The help and support of the Cancer Prevention and Education Society is also gratefully acknowledged (http://www.cancerpreventionsociety.org).

References

The growing incidence of cancer: Role of lifestyle and screening detection (Review)

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Received December 15, 2006; Accepted February 15, 2007

Abstract. The increasing incidence of a variety of cancers after the Second World War confronts scientists with the question of their origin. In Western countries, expansion and ageing of the population, as well as progress in cancer detection using new diagnostic and screening tests cannot fully account for the observed growing incidence of cancer. Our hypothesis is that environmental factors play a more important role in cancer genesis than it is usually agreed: i) over the last 2-3 decades, alcohol consumption and tobacco smoking in men have significantly decreased; ii) obesity is increasing in many countries, but the growing incidence of cancer also concerns cancers not related to obesity nor to other lifestyle-related factors; iii) there is evidence that the environment has changed over the same time scale as the recent rise in cancer incidence, and that this change included the accumulation of many new carcinogenic factors in the environment; iv) genetic susceptibility to cancer due to genetic polymorphism cannot have changed over one generation and actually favours the role of exogenous factors through gene-environment interactions; v) age is not the unique factor to be considered since the rising incidence of cancers is seen across all age categories, including children; vi) the fetus is specifically vulnerable to exogenous factors. A fetal exposure during a critical window period may explain why current epidemiological studies may be negative in adults. We therefore propose that the involuntary exposure to many carcinogens in the environment contributes to the rising trend in cancer incidence.

Contents

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2. Role of lifestyle factors in inducing cancers
3. Epidemiological arguments in favour of the role of the environment in the current growing incidence of cancer
4. Modifications of endogenous factors cannot account for the currently growing cancer incidence

1. Introduction

The overall incidence of cancer is increasing worldwide. Since 1990, global cancer incidence has risen by 19%, while mortality rates from all cancers fell by 17% in persons aged 30-69 and rose by 0.4% in those aged 70 and over (1-3). With an estimated 2.9 million new cases and 1.7 million deaths each year cancer remains an important public health problem in Europe (4). In France since 1980, cancer incidence rate has risen by 30%, as in many other countries (Fig. 1). In the USA, as in several other developed countries, 50% of men and over 30% of women can expect to develop cancer during their lifetime. In the 1950s the lifetime risk was about 1 in 4 (5). A similar evolution is observed in many countries in
Europe. In Western countries, although mortality has declined, cancer is now the second leading cause of death overall and the leading cause of death under the age of 75. According to WHO, worldwide cancer burden is set to increase by as much as 50% by the year 2020, unless further preventive measures are put into practice (6).

There are currently two opposite interpretations of the growing incidence of cancer. The first one considers that environmental pollutants can only make a minor contribution to overall cancer incidence changes and therefore that increase in the size and ageing of the population, lifestyle influences such as smoking, alcohol consumption and diet, and new progress in diagnosis and screening procedures can explain the current increased cancer incidence (7-9). Conversely, the second interpretation, considering that these arguments are not sufficient, estimates that in addition to these factors, there is a contribution from the environment and that involuntary exposure to diverse pollutants may be involved (5,10-13).

The definition of environment varies according to authors. Usually, it refers to the physical, chemical and biotic factors that act upon an individual, and therefore include social and cultural conditions. Geneticists consider all factors that are not innate and therefore, include lifestyle-related factors among environmental factors. We focus here on physical, chemical and biological agents, which may be present in the surroundings of individuals. By contrast, behavioural habits such as smoking, alcohol consumption and diet are excluded from the definition (14).

In a recent report, mortality from 12 types of cancer in 7 World Bank regions were attributed to 9 risk factors, among which 5 result from lifestyle, 2 from viral infection and 2 from air pollution (3). However, all together, these 9 risk factors account for 39-41% of all cancers. So, they are not representative of all presumed risk factors involved in carcinogenesis. The present overview focuses on Western countries. It aims at analyzing new environmental risk factors, discussing the plausibility of their causal effect in the genesis of cancers. We propose that the involuntary exposure to many carcinogens in the environment contributes to the rising trend in cancer incidence in high-income countries.

### 2. Role of lifestyle factors in inducing cancers

It is well agreed that smoking and to a lesser extent alcohol consumption, diet imbalance, obesity and lack of physical exercise are contributing factors to cancer in high-income countries. We analyze these factors and discuss their pertinence and magnitude of effect.

#### Tobacco smoking

Smoking is indeed a major concern. Because tobacco smoke and tar contain mutagenic substances, including Polycyclic Aromatic Hydrocarbons (PAH) and nitrosamines, smoking is a major factor contributing to human carcinogenesis and one of the best determined (Table I). As underlined by many authors, smoking is a risk factor for several types of cancers, mainly lung cancers and cancers of the upper aero-

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Table I. Percentage age of cancers attributable to alcohol and smoking.

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*According to English et al (15).
digestive tract (UADT) (including cancers of the oral cavity, nasal cavities and sinuses, pharynx and larynx), but also, to a certain extent, esophagus, stomach, pancreas, liver, bladder, kidney and cervical cancers, as well as myeloid leukemia (15,16). Because many of these cancers are associated with a poor prognosis, smoking remains a major cause of cancer mortality. In high-income countries, the mean Population Attributable Fraction (PAF) for tobacco smoking in both sexes combined is estimated to be 25-30% of the overall cancer mortality (17). However, because many of these cancers are generally of poor prognosis, PAF related to overall cancer incidence is lower, probably in the order of 20-25% (12). Indeed a major question remains to determine the different factors which contribute to the approximately 70-75% of cancers not related to smoking.

Alcohol consumption. In contrast with PAH and other carcinogenic molecules found in tobacco smoke and tar, ethyl alcohol is not per se a molecule with mutagenic properties, but acts mainly as a cocarcinogen. On the basis of epidemiological data, alcohol has nevertheless been classified as a human carcinogen (18). Indeed alcohol can potentiate the carcinogenic effects associated with smoking or other factors (19) through a cocarcinogenic effect, which accounts for amplification of UADT and esophageal cancer incidence. However, an elevated risk of UADT cancers in the absence of tobacco smoking and of non-tobacco-associated cancers has been observed (Table I, 18). These observations strongly suggest that in such cases, alcohol consumption may be associated with other carcinogenic factors. The mechanism of action of ethanol is not clear. In addition to its predominant cocarcinogenic effect, ethanol has been thought to be associated with some promoting effect. Here we clearly distinguish cocarcinogens from promoters. A cocarcinogen is a molecule which can activate or enhance the action of a carcinogen be it a mutagen or a promoter (20). On the other hand, a promoter is a molecule which stimulates the division of cells and may promote loss of differentiation and apoptosis induction, be the cells mutated or not (21). Among the cocarcinogenic effects of alcohol are the depletion of detoxifying molecules such as glutathione and the induction of the hepatic cytochrome P450 2E1 (CYP2E1) enzyme, leading to the activation of procarcinogens into carcinogens (22,23). By contrast, a promoting effect for alcohol, through immunosuppression induction has been suggested (24). However, this hypothesis has never been validated through pertinent toxicological and epidemiological studies. In addition, because induction of CYP2E1 in the liver may result in the metabolising of ethanol into acetaldehyde, thus leading to the production of mutagenic free radicals, it has been postulated that ethanol may also contribute to initiate specifically hepatocellular carcinoma (HCC) through mutagenesis (25). Yet, this hypothesis needs to be validated. Furthermore, due to a decrease in alcohol consumption over the last 20 years, PAF for alcohol-related cancers is only 4% in high-income countries (3). We therefore conclude that the presumed carcinogenic effect of ethanol needs to be clarified by new toxicological and epidemiological studies, and that overall, because of its trends to decrease, alcohol consumption cannot be a factor related to the recent growing incidence of cancers.

Diet. Several studies have shown that in highly developed countries, food intake imbalance, rich in calories and animal fat and low in fibre, in other words, rich in red meat and poor in fruit and vegetables, is a factor that fosters the occurrence of some cancers (colon, prostate, endometrium and breast) and conversely that high intake of fruits and vegetables has a protective anticancer effect (26,27). Migrant studies strongly suggest that lifestyle-related diets can affect the genesis of the aforementioned cancers (2,28-30). They cannot however rule out the possibility of other associated causal factors. A common interpretation is that increased animal fat intake, rich in polyunsaturated fatty acids, can generate mutagenic free radicals by increasing oxidative stress (31), while diets rich in fruit and vegetables, because they contain many natural antioxidants, can yield an anticancer protection (32-34). We question the magnitude and interpretation of these presumed effects. PAF for cancers related to low fruit and vegetable intake is estimated to be only 3% of cancer mortality in Western countries (3). Furthermore, experimental animal studies have not proven that high fat diet can initiate cancers, but rather that fatty diets can be associated with a cocarcinogenic effect through the induction of the cytochrome P450 system (35). Identification of mutagenic substances associated with cooking of high fat diet has been the object of many efforts. Pyrolysis of aromatic amino-acids and of fatty acids associated with grilled meat has been suspected to be involved in mutagenesis, leading to the hypothesis that heterocyclic aromatic amines (HAAs) and polycyclic aromatic hydrocarbons (PAH) respectively could play a role in cancer initiation (36-38). Some epidemiological studies support this hypothesis, whereas others do not. Such discrepancy may depend on genetic susceptibility (39). Because these studies concern specific selected samples of the population, a major question is to what extent grilled meat (containing HAAs and/or PAH) could impact carcinogenesis in the general population. Furthermore, on the basis on epidemiological and biological data, the role of dietary fat in carcinogenesis is not so clearly defined as usually agreed. Many epidemiological studies testing the presumed role of animal fat in the genesis of cancer are controversial (40-42). An explanation could be that these studies have not been evaluated by taking into account genetic polymorphism and/or continuous induction of CYP450 together with duration of exposure. Although it has been shown that animal fat intake may be associated with colorectal cancer occurrence, it has never been proven that fat per se can initiate carcinogenic effects (43,44). In fact, because diets rich in fatty acids are generally associated with low fruit and vegetable intake, it is indeed quite difficult to disentangle the two effects in epidemiological studies. While it is suggested that food imbalance may act through a direct cocarcinogenic or even indirect promoting mechanism, the hypothesis that fibre in a well-balanced diet (rich in fruit and vegetables) plays a protective role by inhibiting the effect of carcinogens possibly contaminating food or being added to it, is put forward (45,46).

Overweight, obesity and sedentariness. Overweight, obesity and sedentariness have been incriminated as risk factors for cancer (47,48). Recent studies in the USA have shown that
obesity associated with some cancers can worsen mortality (49). Indeed, because obesity by itself increases mortality, these studies do not prove that obesity per se is a factor involved in cancer mortality. However, in many studies, obesity was found to be associated with an increased incidence of several cancer types (50,51) with the exception of lymphoma (52) and childhood cancers (53). Consequently, aside from these cancers, a recent hypothesis is that the observed increase of incidence of several cancer types, such as breast, colon, liver or kidney cancers may be partially due to obesity (54). However, in Western countries, PAF for obesity-associated cancers and for cancers associated with physical inactivity are only 3% and 2% respectively for cancer mortality (3). Thus, as for fatty diets, the role of obesity in carcinogenesis is not clear. Indeed a promoting mechanism whereby obesity could be a risk factor through a modification of the hormonal milieu remains hypothetical (48). Moreover, it has never been demonstrated that excess weight and obesity can initiate cancer. They can, however, indirectly contribute to cancer genesis through a progressive accumulation of chemical carcinogens in adipose tissue. We have clearly shown that lipophilic organic xenomolecules such as benzo[a]pyrene can accumulate in adipose tissue (55) and therefore, that this tissue should be considered as a reservoir for lipophilic xenomolecules including persistent organic pollutants such as dioxins and PCBs (56) from which they are released into the plasma, where they can be detected at doses positively correlated with the body mass index (57). We have clearly demonstrated that benzo[a]pyrene can favor obesity in mice by impairing β-adrenergic stimulation of adipose tissue lipolysis (56). We therefore hypothesize that some carcinogenic molecules may be involved both in obesity and cancer genesis. Such mechanism seems to have been recently suggested for tributyltin an endocrine disruptor associated with carcinogenesis (58) which have been shown to increase adipose mass (59). Since obesity has been found to be associated with several types of cancer, our observation allows to consider that factors other than food intake imbalance and abnormal diet may be involved in carcinogenesis. In addition, a high number of molecules, rated as carcinogenic, probably carcinogenic or possibly carcinogenic to humans, belonging respectively to the IARC’s groups 1, 2 A and 2 B for the
Evaluation of carcinogenicity to humans (60), can bio-accumulate in the organism and may contribute also to carcinogenesis. We are therefore led to the conclusion that, in addition to classical lifestyle-related risk factors, other carcinogenic factors found in the environment could also play a major role in the genesis of cancers.

3. Epidemiological arguments in favour of the role of the environment in the current growing incidence of cancer

The interpretation of the currently growing incidence of cancer shows a divergence of opinions among experts. Some of them, referring to the initial study of Doll and Peto (61) and taking into account ageing of the population and the recent improvement of diagnostic and screening techniques, consider that the main causes of cancer are still related to our lifestyle and that the current growing incidence of cancer is due both to the increase of population life expectancy and the detection of small tumors, which normally will have never developed into symptomatic true cancers. Conversely, other experts referring to the most recent epidemiological and toxicological data emphasize environmental carcinogenic factors (5,11-13). This is the issue we attempt to address hereby, based on epidemiological considerations.

Decrease in tobacco and alcohol consumption. The Doll and Peto study dates back to 1981 and is based on earlier US epidemiological data. Yet, since 1981, our environment has been greatly modified. Alcohol consumption has been in the decline in all countries except in Nordic countries, so it cannot explain the growing incidence of cancers in non-Nordic countries. In addition, smoking for men decreased in all countries (Figs. 2 and 3), so it cannot be a further explanation of the growing incidence of cancers. Though mortality due to lung cancer has increased in men since the last world war in many countries and more recently in women, at the same time tobacco consumption and the proportion of regular smokers have decreased in men in several developed countries, whereas it has progressively increased in women (62). This observation is worth discussing. The analysis in Fig. 4 shows that in France, increase in mortality due to lung cancer in men has slowed down since 1990 and currently tends to level off, which suggests that mortality could drop sharply in years to come, if a stringent policy against smoking is maintained, as any epidemiological translation of reducing smoking requires several decades before its health impact becomes apparent. This is indeed the case today in countries that have launched a real fight against smoking many years ago. However, because PAF for tobacco smoking-associated lung cancer mortality is approximately 90% for men and 70% for women in industrialized countries (63) and probably lower for incidence, i.e. in the order of 80% and 60% respectively, it clearly appears that lung cancers are not exclusively related to tobacco smoking (64-66). Likewise, recent epidemiological data concerning cancers partially related to tobacco smoking, such as bladder and renal cell carcinoma, need to be interpreted in the light of other causal factors. While over the last two decades, incidence of bladder cancer is decreasing in the UK, possibly because of a reduction of smoking, paradoxically it is increasing in France and is stable in the USA, although smoking is also decreasing (Figs. 2 and 5). A similar trend is observed with renal cell carcinoma. Incidence is growing in the UK, France and in the USA, while tobacco smoking is decreasing in these countries (Figs. 2 and 5). This strongly suggests that for kidney carcinoma as well as bladder carcinoma, carcinogenic factors other than smoking have recently emerged. A similar paradoxical picture exists for HCC. Although the incidence of UADT and esophagus alcohol-related cancers have markedly declined over the past decades in many European countries including France (Table I, Fig. 6), mainly due to a decrease in alcohol consumption, incidence of HCC has increased. The currently growing incidence of HCC could therefore be the consequence of other oncogenic factors, such as viral hepatitis B and C (67,68) and/or chemical carcinogens (69,70).

Finally, a basic observation is that the incidence of and mortality from cancers strongly related to tobacco and/or alcohol consumption have been decreasing over the last two decades, while the incidence of cancers not related to tobacco and/or alcohol consumption or to obesity, have been increasing.
This figure reversal characterizes many industrialized Western countries in Europe and in the USA, where the incidence of cancers non-related or weakly related to alcohol and/or tobacco consumption exists (71,72). This increasing incidence and thus the increased risk of cancer, mainly concerns breast cancer in women and prostate cancer in men, but also thyroid cancer, as well as non-lifestyle related cancers including melanoma, mesothelioma, brain tumors, leukemias and lymphomas in adults of both sexes, testicular cancers in young adults and childhood cancers (Figs. 1 and 7).

Impact of new diagnostic and screening methods. Over the last two decades, in Europe and North America, the mean estimated number of yearly cancer cases has approximately doubled for breast cancer (73,74), more or less doubled for prostate cancer (74,75) and more or less doubled for thyroid cancer (76) depending on the country considered. Simultaneously, progress in diagnostic and screening techniques including mammography for breast cancer, cervical smears for cervical cancer, PSA for prostate cancer and ultrasonography for thyroid cancer has emerged allowing detection of small tumors for these four cancer categories (77-80). Clearly, the marked rise in incidence of these cancers with the exception of cervical cancers which has drastically declined over the last decades (81) may be due in part to the detection of latent tumors which may have never progressed into symptomatic cancers (76,82,83). However, although this incidence increase can be partly explained through the recent generalization of screening tests, we assume that other factors do occur for the following reasons: i) with the exception of some very slightly invasive and slowly progressing cancers, any truly invasive cancer almost always converts into a symptomatic disease and consequently is recognized clinically. A significant number of cancers that were not screened 20 years ago were thus probably diagnosed, meaning that in the case of good cancer registries, there cannot be a deficit in reporting; ii) the current screening tests improve early detection of cancers and thus most probably improve prognosis. Indeed, screening for cancers which are detected at a really invasive stage (breast cancer for example) can only influence mortality. On the other hand, impact on reduced incidence can only be assumed for cancers screened at a pre-invasive stage (cervix and colon cancers for example). The current tests should therefore influence mortality rather than incidence unless one considers the possibility of numerous false positive tests, an hypothesis which cannot be substantiated, due to the systematic carrying out and analysis of tissue biopsies showing invasive cancers. This is the case in particular for prostatic cancer. Careful analysis of biopsies revealed that screened cases were associated with the same Gleason grading as non-screened cases, meaning...
that screened cases carry the same histoprognosis as non-screened cases (79); iii) consequently, as a result of screening, a clear decrease in mortality in countries that systematically used screening tests should have been expected. Unfortunately, except for cervical cancer, it is not the case. So, for breast carcinoma, since the use in the late 1980s of systematic screening in 16 European countries, where cancer incidence was increasing, cancer mortality is either stable or slowly decreasing (84). This indicates that part of the increased number of new screened cases was probably related to truly malignant cancers and that screening methods are not sufficient to eradicate cancer mortality. This emerging new concept has been recently debated (85,86). In fact, screening can influence mortality in the detection of both invasive cancers and of pre-cancerous lesions (87,88). In countries that did not use systematic, but rather opportunistic screening, breast cancer incidence is growing, while cancer mortality is either increasing or stable. This indicates that screening may not be efficient, but that the growing incidence of cancer is not related to precancerous or smoldering invasive cancers, but to truly malignant cancers (89); iv) in countries or regions where the incidence rates of breast, prostate or thyroid cancers have been historically low and where there has been no systematically performed screening test detection, increased incidence rates of these cancers is now observed (2,75,90); v) in many countries, the increased incidence of these cancers is such that it is very unlikely that all new cases could be solely due to improvements in diagnosis and screening test procedures (Figs. 7 and 8); vi) a careful analysis of cancer registries of countries that have systematically collected all new cancer cases during a sufficiently long period, i.e. before and after the introduction of new screening tests supports this hypothesis: this is the case in Norway. Fig. 9 relates to the evolution of incidence rates for breast, prostate and thyroid cancers since 1955 in Norway (adapted from Institute of Population-based cancer Research - The Cancer Registry of Norway).
cancers for which no screening test has been developed over the last 20 years: this is the case for testicular cancers as well as for melanoma, lymphoma, leukemia and childhood cancers. Therefore, we theorize that the increased risk of cancer corresponds to a genuine phenomenon from a biological, epidemiological, medical and public health point of view.

4. Modifications of endogenous factors cannot account for the currently growing cancer incidence

Before considering our hypothesis plausible according to which the involuntary exposure to many carcinogens in the environment greatly contributes to the genesis of cancer, a basic question is to examine whether endogenous factors might have been implicated to account for the current growing incidence of cancer and to what extent they might have been involved. This issue is thus worth addressing at a genetic and biological level and consequently focuses more precisely on expanded life expectancy and ageing, as the growing burden of cancer in elderly people could explain the growing incidence of cancer.

**Genetic versus environmental influences.** Cancer is generally recognized as a multistage disease involving accumulation of a critical number of mutations within a stem cell (91). The discovery of oncogenes, tumor suppressor genes, DNA repair genes and cancer susceptibility genes has led to the concept that carcinogenesis is a pure endogenous genetic process (92,93). Clearly, this concept has to be revised, because causation of cancer must be distinguished from its consequences, i.e. the disease itself. Indeed, it has become increasingly evident that due to gene-environment interactions (39), cancer is causally an environmental disease. Two elegant studies documented this new scientific paradigm. Data based on the analysis of co-occurring cancer incidence in a cohort of identical twins have demonstrated that environmental rather than genetic factors predominate in the aetiology of cancer. Theoretically a high level of co-occurrence would have revealed that inheritance is more influential than environmental factors in the causation of cancer. But it is not the case. The study showed that the concordance rate of cancer among identical twins was rather low, indicating that non-genetic influences predominate (94). Moreover, estimation of the relative proportion of genetic and environmental influences for each specific cancer, using a structural equation model, showed that for all cancer types, except thyroid cancers, environmental factors (including lifestyle-factors) predominated (95). It appears therefore, that environmental factors prevail in the aetiology of cancers and consequently that inherited genetic factors are not involved in the current growing incidence of cancer.

**Innate and acquired susceptibility to cancer.** In order to further examine the hypothesis according to which endogenous factors could be considered, it is necessary to question whether the growing incidence of cancer may have resulted from the occurrence of specific inherited mutations of susceptibility genes or from acquired somatic susceptibility within the general population. It is clearly established that in addition to their mutagenic effects, radiation, viruses and chemicals can be cancer promoters via immunosuppression induction. Such a mechanism of acquired susceptibility to cancer is exemplified in selected specific population samples including patients treated with immunosuppressive drugs for organ transplantation (96-99), irradiated people (100,101) or people with HIV infection (102). We do not know to what extent environmental immunosuppressive factors and particularly immunosuppressive chemicals could contribute to acquired susceptibility to cancer within the general population and therefore to what extent, these acquired environmental factors may have been implicated in the current growing incidence of cancer. On the other hand, inherited factors accounting for cancer susceptibility include theoretically specific oncogenes as well as genes involved in the activation or detoxification of carcinogens and repair of DNA damage (39). Three types of arguments discredit the hypothesis according to which an increase in inherited genetic susceptibility could have occurred, accounting for the growing incidence of cancer: i) only a small proportion of cancer follows a Mendelian pattern of inheritance (103,104). Familial cancers arising as a result of highly penetrant mutations be they associated or not with hereditary cancer predisposition syndromes, are unlikely to account for more than 10-15% of all childhood cancers meaning that they represent no more than 0.2% of the total cancer burden (105,106). In addition, inherited tumor suppressor oncogenes, such as BRCA1 and BRCA2 genes in patients with familial breast carcinoma (107) or other inherited susceptibility genes, such as hMSH2, hMLH1, hPMS1, hPMS2 and hMSH6 genes, in Hereditary Non-Polyposis Colorectal Cancer (108) are relatively rare (109) and taken together account for less than 5% of cancers (110). Moreover, despite considerable efforts to identify common less penetrant susceptibility genes for cancer discovery such genes are disappointing (111); ii) by contrast, a more likely situation is that cancers develop as a result of exposure to risk factors in genetically susceptible individuals (112). Indeed, inherited genes that encode enzymes involved in the activation or detoxification of exogenous carcinogenic factors are much more frequent. These genes are polymorphic in nature, meaning that they are a common variant of the enzyme genes (39,113). As a consequence of polymorphism, individual variations in the metabolism of carcinogens account for differences in susceptibility to cancer and could thus impact on the population attributable risk for cancer. Polymorphism has resulted from mutations, which have survived and passed through generations (39). However, it is theoretically and practically impossible to believe that in one generation (25 years), genetic polymorphism would have been modified such that it could have increased so greatly the population’s genetic susceptibility (104); iii) Moreover, while the previous exceptional childhood cancers associated with Mendelian pattern of inheritance are purely related to inherited penetrant endogenous mutations, for all the other inherited cancers, genetic susceptibility just increases the risk of cancers related to exogenous and especially environmental factors (94,114). For example, this is the case for women having one or the other inherited tumor suppressive susceptibility gene BRCA1 or BRCA2. The risk of having breast cancer at age 50 is 24% for those born before 1940, while it is 67% for those born later (107). This means that
since the last world war, a new phenomenon occurred, whether it is related to lifestyle modifications (hormone treatments, later age at first pregnancy, increased number of women with no pregnancy etc.) or to environmental changes.

**Ageing and extended life expectancy.** A major and recurring counter-argument to the environmental concept whereby the current growing incidence of cancer is due to changes in our environment is that we are living longer and cancer incidence increases with age. There is no doubt that life expectancy has been increasing for many decades in Western countries and that cancer incidence increases with age, thereby leading to an increased number of new cases and of deaths from cancer (115-121). The widely accepted opinion according to which extended life expectancy, i.e. increased age, is a major factor to explain the current increase in cancer incidence needs however to be clarified. Crude numbers of cancer burden, be it the number of new cases or the number of deaths are affected by changes in the population size and structure. For comparisons of populations over time, age-standardized rates need to be computed. Therefore age no longer plays a role when examining age-standardized rates and their trends over time or differences across populations. Moreover, from a biological standpoint, the role of ageing in the occurrence of cancer shall be discussed. A basic assumption, which supports the role of age, is that, according to the multistage theory proposed by Armitage and Doll in 1954 (122), people living longer have a greater chance of accumulating the critical number of mutations needed for cell transformation. Indeed the multistage somatic mutations theory is not incompatible with the rising incidence of cancer associated with increasing age, if we assume that many environmental factors are carcinogenic and cancer risk is clearly related to the duration of exposure to exogenous carcinogens. However, in addition to this theory, a second hypothesis has been put forward indicating that besides the extended life duration, ageing by itself could favour cancer, meaning that in addition to mutations induced by exogenous factors, ageing-related endogenous mutations could occur. Consequently, it has been postulated that the currently expanded ageing of the population could be per se a major cause of the observed increased incidence of cancer. It cannot be assumed that ageing by itself is a major contributing factor to cancer genesis for the following reasons: i) in tissue culture, there is no evidence showing that spontaneous (or induced) mutation rates increase according to the number of previous cell generations (123); ii) for a cell to mutate, it needs to divide (124). This basic observation is compulsory. Yet, the widely agreed observation is that the number of stem cells decreases with ageing. It follows thus to conceive that the probability of mutations may be lower in elderly people than in young people, although in the former, the total number of mutations can be higher due to the bioaccumulation process; iii) while it seems clear that ageing can be associated with physiological immunodeficiency and that, in general, immunodeficiency, be it innate or acquired, can favour virus-induced mutagenesis, there is no convincing experimental or clinical data suggesting that ageing per se can spur the initiation of cancers in elderly people. This means that, as much as ageing-related immunodeficiency may play a role in carcinogenesis due to a deficiency in the immunosurveillance system (role of K and NK cells), it would intervene in the promotion phase and not in the initiation phase. From these data, we conclude that ageing per se cannot be a factor, which contributes to initiate cancer, but rather, if we assume that many environmental factors are mutagenic, that cancer risk is clearly related to age, i.e. to duration of exposure to these factors.

**Vulnerability of children with specific reference to fetus.** Indeed, a basic observation that could argue against the previous considerations whereby age is a major contributing factor to the current cancer problem comes from the fact that the increasing cancer incidence is not restricted to any particular age group. Worldwide, age-specific rates of cancer incidence, i.e. the standardized rates for each age group in particular, are rising across the whole age spectrum and particularly in children and young adults. This is the case in the USA as in Europe. According to the NCI, the incidence rate increase for childhood cancers in the USA has been assessed on average at 1% yearly over the past 30 years and this 1% per year figure is also confirmed in Europe (125-127). However, in some countries, it can be higher. For example, in the UK, the overall rate of childhood, adolescent and young adult cancer incidence is increasing by 1.5% per annum (128-130). In Europe, about 1% of all malignant tumors arise in patients younger than 20. Within this age group, the overall incidence rate over the last three decades have been increasing in all ages, but mainly in infants before the age of 3 and in adolescents after the age of 14.

A major question deals with the causal origin of this increase. Considering the presumed role of environmental factors in childhood cancers, there are three periods during which exposures may take place: the preconceptional period (i.e. effects on parental germ cells), the prenatal period (i.e. exposure of the embryo or fetus via the mother’s placenta) and the post-natal period which corresponds to the direct exposure of children to exogenous factors. Childhood exposure to chemicals may result in chemically-induced carcinogenesis as well as in virus-induced carcinogenesis, through chemically-induced immunosuppression. This could be particularly the case in infants, in whom contamination by immunosuppressive chemicals can enhance their physiological postnatal immunologic immaturity (131,132). Infants and children differ also from adults in their direct exposure to environmental toxicants both qualitatively and quantitatively, because proportionally to body weight, they ingest relatively more water and food, and breathe more air than adults (133) and by specific physical activity close to the ground (134). In addition, the high rates of cell proliferation and differentiation as well as their lower capacity of cell detoxication and DNA reparation (135) render cells of the fetus and developing child more susceptible to mutations and/or epigenetic alterations (114). This explains why many clinical studies have demonstrated the extreme vulnerability of the fetus to environmental factors, including viruses (136-138), radiation (139), hormones and chemicals (140-143). Moreover, because there is no protective barrier between the developing fetus and its mother, trans-placental exposure of the fetus to natural or synthetic hormones and chemicals does occur (144-147). In addition, infants may be contaminated during breast-feeding (147). Numerous studies
of prenatal exposure in animal models have confirmed the above observations, indicating that a causal link between environmental carcinogens and cancers exists (148-150). Considering the aetiology of cancer in children, parental exposure to carcinogens is indeed of critical importance. However, although maternal tobacco smoking during pregnancy was first suspected (151), it was not confirmed. There is no consistent association with childhood cancers overall or with specific types, no matter which exposure period is considered. Moreover, a similar negative trend has been put forward for maternal alcohol drinking (152,153). By contrast paternal smoking (154) as well as paternal alcohol drinking before pregnancy (155) were revealed to be associated with a small increase of childhood cancers including acute lymphoid leukemia. This strongly suggests that exposure to classical lifestyle-related factors cannot explain the current growing incidence of childhood cancers, but that preconceptional paternal exposure to carcinogens may be relevant. An important finding, which accounts for the difficulty in interpreting epidemiological data of environmental carcinogenesis is the existence of a critical window period of fetal exposure, during which there is an increased risk of subsequent development of cancer. Based on experimental data, it can be hypothesized that through the perturbation of fetal organogenesis and cell differentiation, there could be a mechanism whereby in utero exposure to low levels of chemicals could lead to the development of several types of cancers, which may occur later in life (156,157). Consequently, in addition to paternal smoking, prenatal exposure and even preconceptional paternal exposure to environmental carcinogens (158) may be causal factors accounting for the growing incidence of childhood cancers, as well as subsequent development of adult cancers.

Finally, contrary to the still prevailing current opinion stating that the growing incidence of cancer is related to classical lifestyle-related factors, improvement of screening tests and/or ageing of the population, we consider that three new concepts have recently emerged, which lead to the conclusion that the bulk of excess cancers in populations exposed to carcinogens, is from the exposure itself in the population at large and not from modification of a large proportion of these factors accounting for the difficulty in interpreting epidemiological data of environmental carcinogenesis is the existence of a critical window period of fetal exposure, during which there is an increased risk of subsequent development of cancer. Based on experimental data, it can be hypothesized that through the perturbation of fetal organogenesis and cell differentiation, there could be a mechanism whereby in utero exposure to low levels of chemicals could lead to the development of several types of cancers, which may occur later in life (156,157). Consequently, in addition to paternal smoking, prenatal exposure and even preconceptional paternal exposure to environmental carcinogens (158) may be causal factors accounting for the growing incidence of childhood cancers, as well as subsequent development of adult cancers.

From this overview, we conclude that lifestyle-related factors with the notable exception of tobacco smoking are not mutagenic, and that screening methods cannot fully account for the currently growing incidence of cancers so that this growing incidence of cancers may result in part from the emergence of new environmental factors. We therefore propose that the causal origin of many cancers cannot be restricted to lifestyle-related factors, but in addition to these factors, depends on many environmental factors including viruses, radiation and chemicals.

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Environmental influences in cancer aetiology

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Abstract

Purpose. The purpose of this review is to inform both scientists and clinicians about the increase in cancer incidence throughout the Western World and to discuss environmental influences in cancer aetiology, in order to stimulate thoughts about plausible aetiological mechanisms and possible preventative measures.

Design. Literature review.

Materials and methods. This review was conducted by searching biomedical databases such as PubMed and Medline. Further research to obtain cancer incidence data involved accessing UK cancer registries, major cancer charities and government statistical records from the Office of National Statistics, the Department of Health, and the Department of Environment, Food and Rural Affairs.

Results. Cancer incidence rates have increased in the Western World and this increased incidence affects the whole age spectrum. Epidemiological studies have provided some evidence of an association between exposure to environmental contaminants such as organochlorines and increased cancer risk. However, many epidemiological studies have been inconclusive. Similar reviews concerning environmental influences in cancer aetiology concluded that exposures to carcinogenic or endocrine-disrupting chemicals exist at concentrations too low or have carcinogenic potential too weak to be considered a major factor in cancer aetiology. However, animal and in vitro studies together with epidemiological evidence discussed in this review would dispute that claim; even if healthy adults are not at risk, it would seem that the developing foetus, infant, child and young adults are at risk. In addition, studies discussed in this review show that low oestrogenic potency cannot be used as a marker of the capability of a chemical to cause oestrogenic responses and endocrine disruption. Genetic polymorphisms, which can predispose people to cancer, may interact with environmental contaminants such as organochlorines and endocrine disrupters, thus providing a modifying effect. Prevention measures have hitherto predominately centred on tobacco smoking cessation and diet education. Anecdotal evidence from practising physicians in pre-industrial and traditional living societies, i.e. Canadian Inuits and Brazilian Indians suggests malignant disease was rare. A relatively new theory other than the somatic mutation theory has been proposed, the main premise being that carcinogenesis is a problem of tissue organization, comparable with organogenesis.

Conclusions. It is feasible that chemical environmental contaminants, in particular synthetic pesticides and organochlorines with endocrine-disrupting properties, could be major factors in cancer aetiology, particularly for hormone-dependent malignancies, such as breast, testicular and prostate cancers. Animal and in vitro studies provide good evidence of a feasible mechanism whereby environmentally relevant levels of organochlorines and substances of low oestrogenic potency can cause endocrine disruption and consequently malignant disease. In addition, low oestrogenic potency should not be
used as a marker of the capability of a chemical to cause oestrogenic responses and endocrine disruption. Preventative measures other than education about tobacco, diet and the promotion of physical activity should be considered. Moreover, it seems to be the most vulnerable members of society: the developing foetus, the developing child and adolescent and the genetically predisposed, who are at risk of developing cancer following involuntary exposure to environmental contaminants. This may be an appropriate time for governments to adopt the precautionary principle until substances to which members of society are involuntarily exposed are proved safe from long-term, low-level effects on human health. The World Health Organization estimates that between 1 and 5% of malignant disease in developed countries is attributable to environmental factors: it is possible that this figure may be underestimated. Anecdotal evidence suggests that cancer may be a disease of industrialization. Further research into the tissue organization field theory may be warranted, as some forms of pre-malignant states are attributed to dysorganogenesis, for example an undescended testis.

**Keywords:** Cancer incidence, epidemiology, cancer and the environment, organochlorines and cancer, persistent organic pollutants and cancer, cancer aetiology, carcinogenesis

**Introduction**

The global burden of cancer is increasing, especially in the developed world. Annually, around 10 million people worldwide will be diagnosed with cancer and a total of 22 million people are current cancer patients. Since 1990, global cancer incidence has risen by 19% [1,2]. According to the World Health Organization (WHO), worldwide cancer rates are set to increase by as much as 50% by the year 2020 unless further preventative measures are put into practice [3].

There is a difference in the distribution of the cancer burden between the developed world (Europe, North America, Australia, New Zealand and Japan) and the developing world (Africa, Latin America, Asia and the Caribbean) (see Figure 1a, b) [1]. The developed world bears the highest cancer burden [1,4]. The incidence of cancer in Europe represents over 25% of the world burden of cancer [5]. The increasing trends for cancer incidence in the developed world can be seen in Figure 2 [6].

The aetiology of malignant disease also differs between the developed and developing world. Twenty-five per cent of cancers in the developing world are a direct result of chronic infection. Infectious agents such as hepatitis B virus, human papillomaviruses and *Helicobacter pylori* are associated with liver cancer, cervical cancer and stomach cancer, respectively. The developed world has a high incidence of tumours that are said to be primarily associated with affluent societies and Western lifestyle, such as lung (tobacco use), breast, prostate and colorectal cancers [1].

In the UK, for the 10 years 1989–1998, some individual tumours such as prostate cancer, breast cancer and non-Hodgkin’s lymphoma (NHL) increased in incidence by 38, 18 and 18%, respectively. Tumours such as lung cancer in males, cervical and stomach cancer have decreased in incidence by 24, 36 and 25%, respectively, over the same time period. However, overall cancer incidence has increased by 1.6% in males and 6.3% in females (see Figure 3) [7]. If the age-standardized incidence rate in England and Wales over the past 30 years is considered (1971–1999), the percentage change for some tumour sites is dramatic (see Figure 4a, b) [8]. The risk of developing cancer in the UK is 35% in males, approximately 1 in 3, and 33% in females, again approximately 1 in 3 [7–9]. Cancer Research UK estimates that around 2% of the UK population (1.2 million) are alive with a diagnosis of cancer [10]. In the USA, the lifetime probability of developing cancer is 1 in 2 for males and 1 in 3 for females [11]. The increasing cancer incidence rate is not restricted to any particular age group: cancer incidence is rising across the whole age spectrum. For
Figure 1. Chart showing a comparison between the number of cancer cases in developed and less developed countries for (a) males and (b) females. Data adapted from [1].
example, in the UK the overall rate of childhood, adolescent and young adult cancer incidence is increasing by 1.5% per annum [12–14]. Figure 5a, b shows the trend for all malignancies except non-malignant melanoma for England and Wales, 1971–1999, for all ages [15]. In 1971, there were 72,685 and 76,026 cases diagnosed in England and Wales for females and males, respectively. In 1999, there were 119,827 and 116,410 cases of malignant disease diagnosed in England and Wales for females and males, respectively [15]. If age-standardized rates (ASR; refers to the standardized European population) are considered for England and Wales, in 1971 the ASR for females was 243.3 per 10^5 population, and in 1999 the ASR was 343.8 per 10^5 population. The ASR for males was 332.1 per 10^5 population in 1971 and 398.0 per 10^5 population in 1999 (see Figure 5a, b) [15].

There are many factors thought to be involved in cancer aetiology: some are well-established known causes of cancer, others are disputed. For example, the link between tobacco use and lung cancer is well known and undisputed [16–19]. However, any link between environmental pesticide exposure and cancer has conflicting evidence [20–25]. The environment is implicated in the majority of cancers. Two recent studies carried out by Lichtenstein et al. [26] and Czene et al. [27] have demonstrated that environmental influences prevail in cancer aetiology. The results from a study observing concurrent cancer incidence in a cohort of identical twins indicated that the environment rather than genetics predominates in the aetiology of cancer [26]. Czene and colleagues developed a structural equation model to calculate statistically significant estimates of the proportion of genetic

Figure 2. Chart showing an increasing trend over time for cancer incidence rates in developed countries. Data taken from [6].
and environmental influences for specific tumour sites. The only tumour site in which genetic influence predominated more than environmental influences was the thyroid [27].

The main factors involved in cancer aetiology are thought to be:

- Tobacco [16–19,28]. Tobacco may be involved in 30% of malignant tumours in the developed world [1].
Diet [29–36].
Alcohol [1,37,38].
Occupation: chemical workers [21], asbestos [39,40], radiation [41–45], benzene [46], dyes [47–50], pesticides [23,51,52], polychlorinated biphenyls (PCBs) [53,54].

Figure 4. Percentage change in the age-standardized rate in England and Wales, 1971–1999, for (a) males and (b) females for major tumour types. Data adapted from [8].

- Diet [29–36].
- Alcohol [1,37,38].
- Occupation: chemical workers [21], asbestos [39,40], radiation [41–45], benzene [46], dyes [47–50], pesticides [23,51,52], polychlorinated biphenyls (PCBs) [53,54].
Medication: anti-cancer drugs [55], hormone replacement therapy [56].
Natural sources: radon [57–59], ultraviolet and cosmic rays [1].
Infectious agents [1,60–63].
Genetic susceptibility [1].
Environmental [1,26,64–70].

Figure 5. Trend for the incidence rate for all malignancies in England and Wales for (a) males, all ages and (b) females, all ages, 1971–1999 [15].
There is discord between researchers into what has facilitated the rise in cancer incidence worldwide, especially in developed countries. The most widely accepted theory is that the increase in cancer incidence is primarily a consequence of an expanding ageing population [10,11,71–74]. The theory is based on the hypothesis that people are living longer, therefore they have a greater chance of accumulating the necessary mutations needed for malignant transformation of cells, according to the multistage theory of carcinogenesis postulated by Armatage & Doll [75], whereby accumulations of mutations in the order of six or seven are needed for malignant transformation of cells. They argued that cancer increases with old age because of the time it takes to acquire enough mutations to render malignant transformation of a cell. A cytogenetic age-distribution study by Moorman et al. [76] did not fit this model. The age distribution of acute myeloid leukaemia patients who had translocations was constant (see Figure 6) [76]. Ames & Gold stated that increasing cancer incidence trends are a consequence of improved diagnostic techniques and screening [77]. However, delays in reporting cancer incidence and errors in the reporting of the data can lead to unreliable cancer incidence rates. If such data are not adjusted correctly, cancer incidence trends may show bias towards a downward trend [78].

Another theory postulated is that the recent rising trend for cancer incidence may in part be a consequence of involuntary exposure to carcinogens in the environment [65,79–83].

Figure 6. A cytogenetic age-distribution study by Morman et al. [76] showing age-specific incidence rates (per million) for de novo acute myeloid leukaemia by karyotype group. Data taken from [76].
This hypothesis is not incompatible with a rising incidence of cancer associated with increasing age. It is widely acknowledged that many environmental pollutants are carcinogens and cancer risk is clearly related to the period of exposure. The International Agency for Research on Cancer (IARC) currently estimates that between 1 and 5% of malignant disease in the developed world is from environmental pollution [1].

In a broad sense, environmental causes of cancer would include tobacco use, lifestyle, diet and occupation. However, this review will define environmental exposure as involuntary exposure to carcinogens. Involuntary exposure implies that the individual has no control over the level of exposure, for example, exposure by means of the diet or through soil, air and water pollution.

This review will examine the current literature concerning environmental influences in cancer aetiology, with particular emphasis on hormonally mediated cancers such as breast, testicular and prostate cancers. NHL and childhood cancer will also be reviewed. Evidence concerning the historical aspect of cancer will also be addressed.

Methodology

Systematic searches of online biomedical databases such as PubMed, BioMed Central, Science Direct and Medline for current literature concerning environmental factors associated with cancer aetiology were made.

Further research to obtain cancer incidence data involved accessing UK cancer registries, major cancer charities and government statistical records from the Office of National Statistics, the Department of Health, and the Department of Environment, Food and Rural Affairs. Overseas government statistical agencies were also contacted and their data accessed. For example, the Cancer Registry of Norway, Statistics Denmark, WHO, IARC, Environmental Protection Agency and National Cancer Institute (both USA).

Cancer incidence data obtained from these sources have been analysed to facilitate the construction of tables and charts in order to graphically demonstrate cancer incidence rates (crude and age standardized).

Historical aspects of cancer

It is difficult to review the evidence available for the historical aspects of cancer. Has cancer been afflicting humans for millennia or is cancer a modern disease facilitated by anthropological activities? Much of the available evidence is subjective and anecdotal.

The oldest written description of cancer dating back to approximately 1600 BC is recorded on The Edwin Smith Papyrus, which describes eight cases of tumours or ulcers of the breast. The writing goes on to state ‘there is no treatment’ [84]. However, two other medical papyruses, the Ebers Papyrus and the Kahun Gynaecological Papyrus, do not mention cancer [84,85].

Bone growths found on skeletal remains of mummies, which are indicative of osteosarcoma and skull destruction similar to that found in head and neck cancer, have been discovered. Evidence of malignant melanoma was found on mummified remains of Peruvian Incas, dating back around 2400 years. The oldest specimen of a human cancer was found in a female skull dating from the Bronze Age (1900–1600 BC). However, the oldest evidence of a hominid malignant tumour (Burkitt’s lymphoma) was found on the remains of a Homo erectus or Austropithecus by Louis Leakey in 1932 [84,86–88].
The word cancer was first used to describe malignant disease by Hippocrates. Blood vessels around malignant tumours reminded him of crab claws. The writings of Hippocrates refer to many different cancer sites [84,88].

Through the Middle Ages and up to the eighteenth century there are many references to malignant disease by doctors and pathologists such as Galen, Stahl, Hofman, John Hunter, Johannes Muller, Karl Thiersch and Rudolph Virchow. John Hunter was the first surgeon to suggest that cancer may be cured by surgery [84,85].

In 1761, John Hill documented the danger of tobacco use in a book titled ‘Cautions against the immoderate use of snuff’. The first evidence of an occupational cause of cancer came from observations by Percivall Pott in 1775. Pott noticed a high incidence of scrotal cancer among young chimney sweeps, which was caused by soot collecting under their scrotum [84,86–88]. Indisputably, cancer is a disease that has always afflicted humans. However, how prevalent was cancer in ancient times and in the pre-industrial era?

An article by Goldsmith [89] addressed this question. Goldsmith reviewed anecdotal recorded evidence from missionaries and some eminent physicians of the late nineteenth and early twentieth centuries. A major source of evidence concerning the prevalence of malignant disease came from a book by Vilhjamur Stefansson [90]. The book cites evidence obtained from authors who were physicians or missionaries in societies that had not changed their way of life for centuries, i.e. traditionally living people and pre-industrial societies. These authors reported a constant pattern of cancer prevalence: malignant disease was remarkably rare or absent. However, one author, Dr William Seaman Bainbridge, who wrote the paper ‘The cancer problem’, observed an adverse change in cancer prevalence as the society became more industrialized [91].

Another example cited by Stefansson that is similar to the observations of Bainbridge comes from studies of the Canadian Inuits by Bulkley [92] and Romig [93]. Bulkley claimed that he did not see a single malignancy in 12 years and any increase in prevalence was influenced by civilization. Romig reported that he also did not observe malignant disease among Inuits living a traditional lifestyle. However, cases of malignant disease became common following transition to a ‘modern lifestyle’.

Stefansson cites many other reports suggesting that cancer was extremely rare among other traditionally living people. One physician, Dr Eugene Payne, spoke of never encountering one case of cancer in over 60,000 patients in Brazil and Ecuador [94]. A Dr Hoffman reported that cancer of the breast was absent in Bolivian Indian women [95].

These reports suggest that although cancer has always been present, the prevalence of cancer has risen through the industrialization and modernization of society.

**Endocrine-responsive tumours**

_Involutionary exposure to environmental pollutants that may be carcinogenic, with particular emphasis on endocrine-disrupting chemicals_

The industrial revolution and the subsequent development of the chemical, nuclear and agricultural industries have produced toxic pollution and novel substances of unknown toxicity. Industry and urbanization resulted in an increase in coal, oil and gas burning, producing toxic smoke and smog. Increasing urban and hospital waste has to be put in landfill sites or incinerated. Chemical production in the last half of the last century produced halogenated molecules such as organochlorines and organofluorines for use in the plastic and pesticide industries as well as others. Evolution has avoided the incorporation of such
molecules in the mainstream of biochemistry and as a consequence they have a general
tendency to be toxic to most forms of life: humans were never meant to be challenged by
these molecules [68]. The nuclear industry involved in producing nuclear power and the
reprocessing of plutonium discharges radioactive waste into the sea and landfill sites. Many of
these chemicals and pollutants are carcinogenic and mutagenic to animals and humans.

Organochlorines such as PCBs, dioxins (the most toxic being 2,3,7,8-tetrachlorodibenzo-
p-dioxin) and pesticides exhibit endocrine-disrupting properties, as do other chemicals
such as phthalates [96–99]. PCBs are no longer produced, but are persistent in the
environment and can show oestrogenic activity, possibly indirectly [100,101]. One major
source of dioxins is the incineration of halogenated plastics such as polyvinylchloride
(PVC). Phthalates are used as plasticizers in PVC products. Organochlorine pesticides are
almost wholly banned in most industrialized countries. However, they are persistent in the
environment. Dioxins and pesticides such as 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane
(DDT) have a molecular structure that shows similarities to oestrogen, and can act
at the oestrogen receptor as an agonist or antagonist (see Figure 7a, b) [102,103].
Metabolites of the fungicide Vinclozolin and the DDT metabolite p,p’-dichlorodiphenyl-
dichloroethylene (p,p’-DDE) have been found to bind to the androgen receptor and
block testosterone-induced cellular responses in vitro [104,105]. Dioxins, pesticides, PCBs
and phthalates may have the potential to be endocrine disrupting and interfere with
developmental processes that are regulated by oestrogenic hormones and their derivatives
such as testosterone. Table I shows some endocrine-disrupting chemicals, together with
their IARC human carcinogen classification [106].

Organochlorines are ubiquitous in the environment, are lipophilic and bioaccumulate in
adipose tissue [54,107–110]. The main source of organochlorine exposure is from the diet:
the higher up the food chain, the higher the concentration of organochlorines to body
weight [111,112].

There is a myriad of in vitro and animal studies on organochlorines that show endocrine
disruption and carcinogenicity [96,99,106,113–121]. However, are humans exposed to
environmental pollutants in sufficient levels to be a major factor in cancer aetiology? This is
a vexed question! Although PCBs, dioxins, pesticides and phthalates have been shown to
be carcinogenic in animals, many researchers believe that the background levels of these
substances are insufficient to cause adverse effects.

Ames & Gold have written many papers on environmental exposure to chemicals, in
which they conclude that synthetic chemicals at background environmental levels do not
pose a risk. Testing a chemical to deduce carcinogenicity on animals is carried out at the
maximum tolerable dose on adult animals. Ames & Gold suggest that the results of these
tests are being misinterpreted to mean that low doses of synthetic chemicals and industrial
pollutants are relevant to human cancer. They postulate that high-dose rodent tests result
in tissue damage and chronic local cell division, which results in cancer, thus the cancer is
due to local tissue damage rather than the chemical. Ignoring this exaggerates risk. At low-
dose levels, i.e. levels to which humans are exposed, this chronic cell division does not
occur. In a book titled ‘Misconceptions about the causes of cancer’, Chapter 8 is devoted to
misconception nine: Pesticides and other synthetic chemicals are disrupting hormones
[77,122,123]. They discuss the findings of Safe, which suggest that human exposure to
oestrogenic organochlorine residues is tiny when compared with the dietary intake of
naturally occurring endocrine-active chemicals (phytoestrogens) in fruits and vegetables,
and therefore any risk to health from synthetic pesticides is minuscule, because far higher
levels of natural phytoestrogens are taken in from the diet [124–126]. Despite the reasoning
Figure 7. (a) Structure of endogenous oestrogens. Adapted from [102]. (b) Structure of dibutylphthalate, bisphenol A, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), dioxin. The molecular similarity of dibutylphthalate, bisphenol A, DDT, p,p'-dichlorodiphenyl-dichloroethylene (DDE) and dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin; TCDD) with oestrogen allows the molecules to act at the oestrogen receptor as an agonist or antagonist [102,103]. The DDT metabolite DDE and the vinclozolin metabolite vinclosolin have been shown to bind to androgen receptors [103,104].
of Ames & Gold, it is feasible that certain chemicals may well be dangerous at current environmentally relevant levels; this is discussed in a later section.

Xenoestrogens and endocrine disruption

To address the question of whether synthetic xenoestrogens pose a risk to human health, oestrogen metabolism and bioavailability need to be discussed. There are three main endogenous oestrogens produced primarily by the female ovaries: 17β-oestradiol (E2), oestrone (E1), which is interconvertable with oestradiol, and oestriol (E3), which is synthesized from oestrone, which is thought to be a partial agonist of the oestrogen receptor. 17β-oestradiol is the most abundant and most potent oestrogen. Following secretion into the blood, the free form of oestrogen is usually only a small fraction of the total oestrogen in plasma: oestrogens are carried bound to various plasma proteins such as albumin and sex hormone binding globulin (SHBG). Bound and free oestrogens in plasma are in dynamic equilibrium [127]. Endogenous oestrogen levels increase during pregnancy.

Table I. Endocrine disrupters and their carcinogenic classifications. Adapted from [106] (Permission to use table granted by Oxford University Press, Japanese Journal of Clinical Oncology and the author, Professor Hiroyuki Tsuda.

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<th>IARC assessment</th>
<th>Humans</th>
<th>Animals</th>
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<tbody>
<tr>
<td><strong>A. Xenobiotics mimicking or antagonizing sex hormones</strong></td>
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<td>1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT)</td>
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<td>Polychlorinated biphenyls (PCBs)</td>
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<td>Tetrachloro-p-dioxin (TCDD)</td>
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<td>Phenols and phthalates</td>
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<td>Butylated hydroxyanisole (BHA)</td>
<td>2B</td>
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<td>Bisphenol A</td>
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<td>Di(2-ethylhexy) phthalate (DEHP)</td>
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<td>1,4-Dioxane</td>
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<td>Tin compounds: tributyl tin (TBT)</td>
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<td>Phenylmethyl-substituted siloxanes: cyclotetrasiloxanes</td>
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<td><strong>B. Natural compounds mimicking or antagonizing sex hormones</strong></td>
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<td>Isoflavanoids (glucoside conjugates)</td>
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<td>Genistein</td>
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<td>Daidzein</td>
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<td>Zearaleone</td>
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<td><strong>C. Substances affecting thyroid function</strong></td>
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<td>Goitrogens</td>
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<td>Aminotriazole</td>
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<td>Thiouracil</td>
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<td><strong>D. Modulators causing mineral corticosteroid imbalance</strong></td>
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<td>Glycyrrhizic acid (from liquorice)</td>
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IARC, International Agency for Research on Cancer.
IARC assessment (to humans): 1, carcinogenic; 2A, possibly carcinogenic; 3, not classifiable as to its carcinogenicity; I, inadequate evidence; S, sufficient evidence; L, limited evidence; ND, no adequate data.
However, SHBG levels also increase, which means that free oestrogen levels in plasma remain fairly constant. This ensures that maternal oestrogen is not readily bioavailable to the foetus. However, environmental oestrogens do pass freely over the placenta: diethylstilboestrol (DES) crosses the primate placenta in an unconjugated form [128,129]; bisphenol A, PCBs and other organochlorines have been shown to pass directly across the human, primate and F344/DuCrj (Fischer) rat placenta [130–135].

Phytoestrogens are ingested via the diet and there is some evidence that these weakly oestrogenic compounds may confer a protective role against cancer [136–139]. A study by Bradlow and colleagues [140] provides an insight into the possible mechanism by which the relatively tiny amount of synthetic pesticides may be carcinogenic compared with the relatively huge amounts of natural oestrogenic pesticides. They studied the effect of natural and synthetic pesticides on oestrogen metabolism. Oestrogen metabolism proceeds down two mutually exclusive pathways: the catechol pathway, which produces oestrogen-2-hydroxyestrone, and an alternative pathway that yields 16a-hydroxyestrone. The catechol oestrogen-2-hydroxyestrone is weakly anti-oestrogenic and non-genotoxic. However, 16a-hydroxyestrone is a potent oestrogen, tumorigenic, genotoxic and induces cell proliferation. Bradlow et al. studied the ratio of 16a-hydroxyestrone/oestrogen-2-hydroxyestrone in oestrogen receptor-positive MCF-7 human breast cells after treatment with 7, 12-dimethylbenzen[a]anthracine (DMBA) and linoleic acid as positive tumorigenic controls; indole-3-carbinol and eicosapentenoic acid as negative controls; and organochlorine pesticides (DDT, Atrazine, γ-benzene hexachloride, Kepone, coplanar PCBs and endosulphans I and II). The results showed that all the organochlorines tested in the study decreased the amount of 2-hydroxyestrone produced and significantly increased the amount of 16a-hydroxyestrone produced by three- to four-fold relative to negative control cells. DDT, Kepone and Atrazine treatment caused a greater conversion to 16a-hydroxyestrone (seven-fold) and lower conversion to 2-hydroxyestrone than the positive controls, which were known carcinogens. Indole-3-carbinol and eicosapentenoic acid treatment resulted in ratios of 1/10 and 1/2 that of DMBA, respectively, indirectly inhibiting 16a-hydroxyestrone production by increasing C-2-hydroxylation [140].

Bradlow et al. pointed out that a previous study had shown that 16a-hydroxyestrone is genotoxic to normal mammary epithelium, and a raised ratio of 16a-hydroxyestrone is associated with breast and other cancers in animals [141]. Conversely, the oestrogen metabolite oestrogen-2-hydroxyestrone has not been found to be carcinogenic and is weakly anti-oestrogenic, and it may even mediate a protective effect [142]. Animal and human in vivo studies found that diets rich in compounds that stimulate oestrogen-2-hydroxyestrone, particularly cruciferous vegetables, which are high in indole-3-carbinol, are protective against cancers such as breast and colon cancer [136–138,143,144].

Although the catechol oestrogen-2-hydroxyestrone is not genotoxic, some catechols derived from quinines and semiquinones have been implicated in cancer aetiology. The catechols 4-hydroxyestradiol, 2-hydroxyestradiol and 2-hydroxyestrone are the three most common catechol oestrogens and only 4-hydroxyestradiol has been shown to be carcinogenic in the male Syrian hamster. No evidence has yet been found in humans to suggest that 4-hydroxyestradiol is formed in vivo [140].

Ames et al. point out that Americans ingest 5000–10,000 different natural pesticides and their metabolites, many of which have oestrogenic activity, and each day this intake amounts to approximately 1500 mg of natural pesticides; some 10,000 times more than the 0.01 mg of synthetic pesticides ingested per day [124]. However, it may be feasible that the 1500 mg of
natural pesticides (phytoestrogens) may provide a protective effect against cancer and the 0.01 mg of synthetic pesticides may be involved in cancer aetiology, mediated by the mechanism described by Bradlow et al. [140]. In addition, humans co-evolved with plants that produced novel phytoestrogens and were able to adapt to exposure of these compounds by a progressive ability to safely metabolize compounds that may have initially been toxic. Organochlorine pesticides bioaccumulate over time; this infers that the enzymes required for effective metabolism and excretion of such compounds are either inefficient or not present [145]. In addition, it is possible for a single pesticide to have thousands of congeners, making toxicological testing very difficult [146].

The oestrogen receptor binding pocket is relatively open and has therefore been described as promiscuous. Phenolic, planar compounds with two oxygen-containing moieties, which are around 1.1–1.2 nm apart, will fit into the binding pocket. In addition to endogenous oestrogens, non-steroidal compounds, for example, DES and many synthetic environmental oestrogens and plant polyphenols (isoflavones, coumestrol) can act as oestrogen receptor ligands [147]. The oestrogen receptor historically only had to distinguish between natural endogenous hormones and this is the reason for the ‘looseness’ of the receptor. The looseness of the receptor infers that before anthropogenic activities contaminated the environment, the only compounds that acted as ligands at the oestrogen receptor were natural oestrogens [145].

Changes in the bioavailability of endogenous oestrogens by exogenous oestrogens can also be a factor that modulates oestrogen toxicity. Serum oestrogens are strongly bound to the serum proteins albumin and SHBG, so that around 5% is circulating unbound or free. The bioavailability of oestrogen is determined by the extent of this protein binding. SHBG does not avidly bind to environmental oestrogens and exogenous oestrogenic compounds can affect SHBG binding to endogenous oestrogens, thus providing a mechanism whereby exogenous oestrogen modulates endogenous oestrogen activity [148].

In a review of his ‘oestrogen hypothesis’, Sharpe examined data relevant to the hypothesis that oestrogenic compounds may perturb male reproductive tract development. Consequently, compounds exhibiting oestrogenic activity may be a factor in testicular dysgenesis syndrome (TDS), a collection of male reproductive tract disorders, such as testicular cancer, cryptorchidism, low sperm count and hypospadias. Compounds that have been identified as environmental oestrogens have weak intrinsic oestrogenic activity. If these are compared with the known oestrogenic transplacental carcinogen DES, Sharpe concluded that it is unlikely that weak environmental oestrogens could induce TDS. His conclusion was based on a study that showed that exposure to DES needs to be at doses in excess of 50 μg kg^{-1} day^{-1} to induce reproductive tract abnormalities [115]. Sharpe stated: ‘based on present understanding, it seems unlikely that altered human exposure to weak oestrogenic compounds can account for the possible increasing incidence of male reproductive tract disorders’. However, he added the caveat: ‘this must be considered a tentative conclusion; this does not mean that exposure to environmental chemicals can be ruled out as being involved aetiologically in “testicular dysgenesis syndrome”, as in utero exposure of rats to certain phthalates has been shown to induce a remarkably similar constellation of disorders’ [149–152].

Sharpe cited recent studies in which the findings suggest that reproductive tract disorders in male rats are a consequence of a perturbed oestrogen/androgen balance and not from absolute levels of androgens and oestrogens. Thus, much lower levels of oestrogens could be capable of inducing adverse effects if concomitantly androgens are suppressed or production is stopped [115,150,153].
A study by vom Saal and colleagues [121] investigated the effects of \textit{in vivo} exposure to high and low (environmentally relevant) doses of oestradiol and DES on the male mouse foetus. They found that low doses of DES (0.02, 0.2 and 2.0 ng g\(^{-1}\) day\(^{-1}\)) resulted in a significant increase in adult prostate weight and an increase in the number of androgen receptors, when compared with control mice. However, high doses of DES (200 ng g\(^{-1}\) day\(^{-1}\)) had the opposite effect: prostate weight was significantly lower than control mice and low-dose treated mice. These effects were also observed for oestradiol, resulting in an inverted U-shape dose–response relationship [121].

Most animal testing is carried out on adult animals and with single chemicals. However, humans are simultaneously exposed to many different chemicals in the environment. Mixtures of chemicals could potentially have synergistic or additive effects. Therefore, traditional toxicological testing may not be adequate for assessing the carcinogenic risk of environmental chemicals [68]. Synergistic and antagonistic effects have been shown when 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and PCBs are administered to rats in varying doses [120].

The US Environmental Protection Agency set up a panel to review low-dose environmental chemicals. The doses that the animals received in the tests had to be lower than the usual animal testing doses or dose levels to which humans are exposed. A subpanel reviewing bisphenol A found that several studies gave credible evidence for low-dose effects. The effects included increased prostate weight in 6-month-old mice and advanced onset of puberty in female mice following \textit{in utero} exposure of 2 or 20 \(\mu\)g kg\(^{-1}\) day\(^{-1}\). In addition, two different strains of rats showed different effects from bisphenol A. F344 rats exhibited low-dose effects on uterine growth and serum prolactin levels. Sprague–Dawley rats exhibited no adverse effects from low-dose bisphenol A [119].

Animals that showed adverse effects to low-dose bisphenol A also showed effects to low-dose DES. Animals that showed no adverse effects to low-dose bisphenol A also had no effects to low-dose DES. However, due to several studies also consistently showing no effects to low-dose bisphenol A, evidence for low-dose bisphenol A is inconclusive. The Environmental Protection Agency has identified areas of research that need to be carried out in order to clarify the situation regarding low-dose bisphenol A [119].

The panel have also reviewed experiments concerning other environmental oestrogens. The definition of a low-dose effect was that a low-dose effect was deemed to have occurred when a non-monotonic dose response (U-shape) resulted in effects that were significant and occurred at a dose lower than the no observed effect level observed by traditional animal testing models. Low-dose effects were observed for oestradiol, DES, merhoxychlor (insecticide), genistein and nonylphenol. For low-dose DES exposure \textit{in utero} at 0.02 \(\mu\)g kg\(^{-1}\) day\(^{-1}\) there is a clear effect on prostate size in mice. Low-dose genistein exposure \textit{in utero} through to puberty resulted in hypothalamic changes and changes in the mammary tissue of male rats [119].

The review panel concluded that the current testing paradigm needs to be revised. Changes may be needed regarding dose selection, the age when animals are evaluated and the endpoints measured [119].

An example of adverse effects on development following exposure to environmental xenoestrogens is in the form of neurotoxicity. In a recent review, human prenatal exposure to PCBs and their effect on neurodevelopment was studied. The authors found that the neonates had impaired reflexes and at 4 years of age deficits in cognitive skills were observed [154]. Other effects on development by PCBs have been reported over the last 10 or 20 years. Sex ratios in humans and fish are declining [155]; male fish [116] and frogs...
[118] are becoming feminized. Some aspects of human development regulated by hormones are showing signs of perturbation. There is increasing incidence of cryptorchidism seen in males [82] and earlier entry into puberty [156].

In human epidemiological studies, many organochlorines, pesticides and other environmental contaminants that show carcinogenic potential following mutagenicity testing have been implicated in cancer aetiology. However, many other studies dispute any link between environmental contaminants such as endocrine-disrupting compounds (except those universally accepted) and cancer aetiology.

Endocrine disruption is just one example of a possible environmental factor that may or may not be involved in cancer aetiology. Other examples include low-level radiation around nuclear installations and coastlines, electromagnetic forces and radon exposure from anthropological activity. In addition, there may be many possible carcinogenic compounds to which people are exposed in household products. This could be construed as voluntary exposure. However, this may be due to a lack of education about specific products or people may have no alternative but to use a product that may contain even a small carcinogenic risk. For example, aromatic amines in permanent hair dyes were shown to increase the risk of bladder cancer by 3.3-fold among regular users relative to non-users in a study by Gago-Dominguez et al. [49]. Occupational exposure to hair dyes was shown to increase bladder cancer risk by five-fold in people who had worked 10 or more years as hairdressers or barbers. A follow-up study showed that the increased risk was confined to people showing the N-acetyltransferase-2 (NAT2) slow acetylator phenotype [48]. However, Nohynek et al. [157] concluded that ‘the weight of evidence suggests that consumer or professional exposure to hair dyes poses no carcinogenic or other human health risks’.

Underarm cosmetics have recently been implicated in the aetiology of breast cancer. Darbre [158] proposed the hypothesis that the chemical constituents of deodorant cosmetics applied to the underarm area can cause breast cancer. Darbre based this hypothesis on observations showing a disproportionately high incidence of breast cancer in the upper outer quadrant of the breast and that the left breast is more prone to the development of cancer than the right breast in both females and males. Darbre implicated parabens as the possible carcinogenic agent in underarm cosmetics. An editorial by Harvey [159] reviewed Darbre’s hypothesis and concluded that: ‘without clear evidence that using weakly oestrogenic compounds in underarm cosmetics is safe; it may be prudent to apply a precautionary principle and replace known oestrogenic formulation excipients and also, in the case of preservative removal, accept shorter shelf lives’.

**Breast cancer**

**Breast cancer incidence**

Worldwide, breast cancer accounts for 10% of the total cancer burden, with an incidence rate of 1,050,000 cases year$^{-1}$ [1]. Almost all cases are found in women; men are 100 times less likely to develop breast cancer [160]. Breast cancer is now the most common cancer among women in developed and developing countries and is described as an epidemic in the world cancer report 2003 [1,161,162]. Worldwide, over a 20-year period, the estimated number of breast cancer cases has doubled [160]. In 1998, the UK breast cancer incidence rate replaced lung cancer as the most common cancer in women and became the most common cancer overall; 15% of the total. In the UK, in 2000 the ASR for breast cancer was 113.9 per 10^5; in terms of cases, there were 40,470 breast cancers diagnosed (30% of all...
cancers in women). The total number of breast cancer cases diagnosed was 40,707; males accounted for 240 of these cases [10].

In England and Wales in 1999, the ASR was 116.9 per 10^5; there were 36,438 cases of breast cancer diagnosed. In 2000, the ASR was 114.0 per 10^5 and there were 33,829 cases diagnosed [15]. However, this fall in incidence rate must be treated with caution because not all the breast cancer cases may have been registered. There is evidence that cancer registries can take many years to fully collate cancer incidence data. Swerdlow [163] found that late registrations can affect published incidence data. Incidence data have been added to publications up to 7 years after data have first been extracted for publication. In the 10 years 1989–1998, breast cancer incidence rose by 18% in the UK. In England and Wales in the period 1971–1999, the percentage change in the ASR of breast cancer was 75% [7,8]. Figure 8 shows the trend for cases, and rates of breast cancer in England and Wales, 1971–1999 [15]. In 1950, the chance of a diagnosis of breast cancer was 1 in 20. In 2000, the risk was 1 in 8 [164]. Breast cancer incidence has been shown to be rising in all of 16 European countries in a study by Botha et al. [165].

Geographical variations and socio-economics are important in breast cancer aetiology [166]. Breast cancer risk is highest in affluent societies: the highest rates are found in North America, Europe and Australasia; the lowest rates are found in Africa and Asia [1,161,162].

Factors involved in breast cancer aetiology

The risk factors involved in breast cancer aetiology include: null parity, late first birth, lack of breast-feeding, early menarche, late menopause, long-term oral contraceptive use, hormone replacement therapy, high calorific diet with reduced physical activity (obesity), alcohol, familial history (BRCA1, BRCA2 and p53 germline mutations), radiation
Epidemiological studies on migrants from countries with a low incidence to countries with a high incidence who subsequently developed breast cancer suggest that environmental factors play a role [1,162,170]. The Westernization of areas within Asia has also been suggested to be involved in the aetiology of breast cancer [171]. High levels of endogenous oestrogen have been implicated in an increased risk of breast cancer [172,173]. In one study in the USA, the well-established risk factors for breast cancer accounted for 47% of cases in the study and 41% of cases in the USA [174]. This suggests that in over half of breast cancer cases, the aetiology is unexplained. Other putative factors are exposure during breast tissue development to environmental contaminants of air, soil and water, such as pesticides, organochlorines, dioxins, PCBs and hexachlorobenzene (HCB). All of these have shown evidence of endocrine-disrupting properties that may directly or indirectly interfere with hormone pathways. Extensive research has taken place into such environmental contaminants to elucidate their possible link with the aetiology of breast cancer. Animal evidence has shown an association between environmental contaminants such as organochlorines and the risk of breast cancer. In addition, endocrine-disrupting substances have been shown to disrupt mammary gland differentiation and development following pre-, peri- and postnatal exposure. This evidence is discussed in a later section (Prenatal Exposure).

Environmental factors and breast cancer aetiology

In 1976, in Seveso, Italy, an industrial explosion resulted in environmental contamination of dioxins: up to 30 kg of the chlorinated dioxin TCDD was deposited in the local environment. Studies examining possible links to the risk of breast cancer in Seveso (10- and 15-year follow-up studies) found no increased risk for breast cancer incidence. However, a 20-year follow-up found a statistically non-significant increased risk for breast cancer mortality among women who lived in the most heavily contaminated areas, which suggested a wide range of individual TCDD exposure within zones. A study examining individual TCDD exposure using data from the Seveso Women’s Health Study found serum TCDD levels for cases who lived in the most contaminated areas ranged from 13 to 1960 ppt. Statistical analysis showed a dose-dependent risk for breast cancer: the hazard ratio for breast cancer associated with a 10-fold increase in serum TCDD levels was significantly increased to 2.1. The authors stated that these results should be considered an early finding because the cohort study was relatively young; the average interview age was 40.8 years [175]. Further epidemiological studies on populations exposed to background levels of environmental contaminants have shown inconsistent and conflicting results.

Epidemiological studies

Epidemiological studies conducted in Long Island, New York, provide an example of these conflicting studies. Long Island has the highest rate of breast cancer in New York State, which causes public concern. Stellman and colleagues [176] conducted a study to determine whether there was an elevated risk for breast cancer associated with organochlorine adipose tissue concentration. They found that adipose tissue concentrations of the organochlorine compounds DDE, PCBs and total pesticides, which included seven species, were not elevated among controls or cases. In addition, no evidence of a dose–response relationship for the organochlorine compounds analysed was found (a significant dose-related increase in risk was observed for the PCB congener 183, which is heptachlorinated). The results conflicted with a previous study, which found an association
between breast cancer risk and levels of PCB congener 118; Stellman and colleagues did not reproduce this result. The mean adipose levels of DDE, total pesticides and PCBs did not differ between control residents from Queens and Long Island. However, interestingly in an individual analysis of $\beta$-hexachlorocyclohexane ($\beta$-HCH) and PCB congener 167, there were significant differences in the mean levels between controls from Queens and Long Island (250 of the control women had benign breast disease) [176]. Although the authors found no association between serum organochlorine levels and an elevated risk for breast cancer, they were concerned that all of the samples showed detectable levels of pesticides and PCBs. This gives cause for concern because pesticides and PCBs have been implicated in the aetiology of a number of other cancer types.

A second study, which made use of blood taken from women from a population-based case–control study conducted on Long Island in order to analyse serum organochlorines, found no association between organochlorine exposure and elevated breast cancer risk. The organochlorines analysed included the pesticides DDE, chlordane and dieldrin. The sum of the four most frequently occurring PCB congeners 118, 153, 138, and 180 was also analysed. In addition, no elevated risk was found for organochlorine exposure among women who were overweight, postmenopausal or long-term residents of Long Island [177]. However, a recent study by Muscat and colleagues [178] in Long Island, which examined adipose concentrations of organochlorine compounds instead of serum organochlorine compounds, found an increased risk of breast cancer recurrence.

As outlined earlier in this section, epidemiological studies investigating associations between exposure to environmental contaminants and an elevated breast cancer risk have produced conflicting results, but have provided valuable data and information for further studies. Breast cancer has probably been the most widely investigated tumour and a link between environmental factors and elevated breast cancer risk has been suggested.

Helzlsouer et al. [179] conducted a nested case–control study in 1999 utilizing women who had donated blood in the 1970s. The study found no association between serum concentrations of DDE, the primary metabolite of DDT, and PCBs and the development of breast cancer up to 20 years later.

Zheng and colleagues [180] carried out a study examining breast adipose tissue HCB levels and breast cancer risk. There was no significant difference in adipose tissue levels of HCB between breast cancer patients and controls with benign breast disease. However, these results could be flawed because the controls were not randomly picked non-breast cancer patients: they were patients with benign breast disease. In addition, the authors reported difficulty in obtaining equal sample sizes from benign breast disease patients and breast cancer patients. In this study, HCB levels were higher in postmenopausal women than in premenopausal women.

A prospective study by Dorgon et al. [181] using the Columbia, Missouri Breast Cancer Serum Bank found no overall association between serum organochlorines (PCBs and pesticides) and elevated breast cancer risk. The results suggested that increased serum levels of organochlorine pesticides (DDT) and PCBs (total) did not increase the risk of breast cancer. However, a positive association was suggested for PCB congeners 118 and 138 when blood was collected close to the time of diagnosis. There was also a significant positive association for HCB, although no dose–response relationship was found. They found no association between DDT and total PCB. The overall conclusion was that the organochlorine compounds analysed were not associated with an increased risk of breast cancer [181]. However, congener-specific studies do show an association: exposure to dioxin-like PCBs increases breast cancer risk.
In a study by Demers et al. [182], the most abundant and persistent PCB congeners (PCB 138, PCB 153, PCB 180) were not linked to breast cancer risk. However, PCB 118 and PCB 156 were individually related to risk. Breast cancer risk was also associated with a total concentration of the three mono-ortho-substituted congeners 105, 118, and 156. An earlier study by Demers et al. [183] suggested that organochlorine exposure may affect the aggressiveness of breast tumours, for example, the risk of lymph node involvement may be increased.

A Norwegian study found no association between organochlorines and increased breast cancer risk [184]. However, the body mass index (BMI) data for the participants were not available to the authors; BMI has an inverse relationship with PCB concentration in serum. Nor did the authors have data on menopausal status. However, they did find an interesting result. Some organochlorines were at lower levels in cases than in controls. Could changes in metabolism in cancer patients be responsible for the difference in organochlorine serum levels compared with controls? Also, the PCB congeners with the most oestrogenic potential are the ones most quickly metabolized. This therefore poses a problem for human studies.

Serum samples taken from women diagnosed with breast cancer and healthy control women in a study by Charlier et al. [185] suggested that certain persistent pollutants may occur in higher concentrations in breast cancer patients than in controls. Charlier et al. found that mean serum levels of total DDT (all DDE and DDT isomers) and HCB were significantly higher for women with breast cancer when compared with control women. In addition, no differences in serum levels of DDT or HCB were found between oestrogen receptor-positive and oestrogen receptor-negative breast cancer patients. Conversely, a study by Hunter et al. [186] found that exposure to high levels of DDE and PCBs was associated with a non-significant lower risk of breast cancer. The median level of DDE was lower among case patients than controls (4.71 vs. 5.35 ppb). Similarly, the median level of PCBs was 4.49 vs. 4.68 ppb for patients and controls, respectively [186].

Many of the epidemiological studies discussed above concerning environmental exposure to organochlorines and the risk of breast cancer are inconclusive. However, improved standardization of studies may help to lead to results that are more conclusive. Studies on human cell lines provide evidence that suggests an association between environmental contaminants and increased breast cancer risk. This is discussed below.

In vitro studies on human breast cancer cell lines have shown associations between environmental contaminants and breast cancer

The tumour suppressor gene BRCA1, which has a role in cell-cycle control and genetic stability in DNA repair, is often down-regulated in sporadic breast cancers. The down-regulation is not thought to be a consequence of a mutation in BRCA1. Expression of BRCA1 is induced by 17β-oestradiol [187,188]. A study by Rattenborg and colleagues [187] examined the effect on BRCA1 expression of TCDD and the PCBs 158, 180. A reporter gene construct carrying the BRCA1 promoter in human breast cancer cell lines MCF-7 (oestrogen receptor positive) and MDA-MB-231 (oestrogen receptor negative) was used to measure the expression of basal BRCA1 and 17β-oestradiol-induced expression. The results from the reporter gene showed that TCDD and the three PCB congeners reduced both basal and 17β-oestradiol expression in both cell lines. These results were confirmed by Northern blot analysis of BRCA1 mRNA in MCF-7 cells. However, the Northern blot analysis of BRCA1 mRNA in MDA-MB-231 cells showed no effect from the TCDD and the three PCB congeners, which suggested the primary
mechanism of action was via the oestrogen receptor. Because the organochlorines tested increased BRCA1 promoter activity, other mechanisms of action must also be considered. The authors concluded that the anti-oestrogenic effect and subsequent down-regulation of BRCA1 could impair DNA repair, cell-cycle control and stress-induced apoptosis and may therefore affect the risk of breast cancer [187]. Another study using the human cell line MCF-7 showed that exposure to β-HCH promotes epigenetic transformation and invasiveness of these cells. β-HCH is a contaminant of the pesticide lindane, which is still in use in the USA. The cells were exposed to β-HCH for 13 months, which resulted in cells with transformation tendencies and transformation-related biochemical changes. The levels of β-HCH used in the study were comparable with levels found in breast adipose tissue [189].

Bradlow and colleagues [140] studied the effect of natural and synthetic pesticides on oestrogen metabolism in MCF-7 human breast cells. This study is discussed in the Xenoestrogens and Endocrine Disruption section of the review. The results suggested a plausible mechanism by which relatively minute amounts of synthetic pesticides compared with natural pesticides could cause cancer [140]. The authors point out that a previous study had shown that 16α-hydroxyestrone is genotoxic to normal mammary epithelium, and a raised ratio of 16α-hydroxyestrone is associated with breast and other cancers in animals [141].

A recent review by Coyle [190] describes a study by Martin and colleagues [191] using MCF-7 breast cancer cells, in which the divalent ions cadmium, copper, cobalt, nickel, lead, mercury, tin and chromium, together with arsenic, selenite and vanadate were shown to have oestrogenic activity. The metals activated responses that were mediated by oestrogen receptor α and the metallo-oestrogens were found to have a greater potency than phytosterogens [191]. A further experiment by Johnson and colleagues [192] investigated the effect of environmentally relevant levels of cadmium on the whole animal. They found that low-dose cadmium induced oestrogen responses in female rats such as increased uterine weights, hyperplasia and hypertrophy of the endometrial lining, and increased mammary epithelial density.

Could genetic polymorphisms make people more susceptible to cancer following exposure to environmental contaminants such as xenoestrogens?

A study carried out to examine the interaction of PCBs with the CYP1A1-MspI and exon 7 polymorphisms among 367 breast cancer case–control pairs, of which 293 were postmenopausal pairs, in the Nurses’ Health Study, concluded that more studies are required on people who may be genetically susceptible to xenoestrogen exposure [193]. The enzyme CYP1A1 has been shown to be induced by PCBs and DNA adducts may form following exposure to PCBs via a pathway involving CYP1A1 [194]. The results of the study showed no evidence of an association of either the variant CYP1A1 genotype or exposure to PCBs with breast cancer risk. In addition, there was no evidence of an association between PCBs and the risk of breast cancer for women with CYP1A1 homozygous wild-type. However, the results did show a borderline statistically significant increased risk of postmenopausal breast cancer among women with high serum PCB levels and at least one variant allele of the CYP1A1-exon 7 genotype when compared with women homozygous for the wild-type allele and with the lowest levels of PCBs [193].

A study by Hoyer et al. [195] was the first to examine whether mutations in the tumour suppressor gene p53 affected organochlorine exposure-related breast cancer risk and survival. The study involved analysing for serum concentrations of organochlorines, which
included DDE, DDT, dieldrin and total PCBs, which were compared between cases and controls while stratifying by \( p53 \) mutation status. The results showed a non-significant three-fold increase in the risk of breast cancer associated with the highest exposure level of dieldrin and PCBs among cases with \( p53 \) mutations. However, for DDT and DDE exposure, no difference was found for breast cancer risk between cases with or without mutant \( p53 \). When the prognostic value of \( p53 \) mutation status and organochlorine exposure was considered, for example relative risk of dying, the only significant result appeared for dieldrin exposure among cases with ‘wild-type’ \( p53 \). The results showed a lack of prognostic value according to \( p53 \) status following organochlorine exposure. However, the results suggested that there is an increased risk of breast cancer in women exposed to dieldrin and total PCBs with mutated \( p53 \) status. The authors concluded that the study suggested that \( p53 \) may have a modifying effect on organochlorine influence on breast cancer risk [195].

In vivo and in vitro studies examining organochlorine exposure and breast cancer risk

The evidence discussed above was largely based on adult exposure to organochlorines. However, as discussed in detail in a later section, in utero exposure to organochlorines or exposure at a time when female secondary sexual development is occurring, may be involved in breast cancer aetiology. During development, high rates of cell proliferation and differentiation leave the child’s cells prone to mutagenic and epigenetic alteration.

Preliminary findings from a study by Palmer and colleagues [196] suggest that women exposed to DES in utero may have an increased risk of developing breast cancer later in life. However, the results were not statistically significant. The cohort was of mean age 43 years, so the authors will be conducting a further follow-up.

In vivo studies using rodents have indicated that exposure to dioxin and other organochlorines in utero may predispose female offspring to breast cancer. Dioxins can disrupt endocrine systems and interfere with the proliferation and differentiation of mouse and rat mammary glands. In addition, dioxin can expand the time that a foetus is most sensitive to prospective carcinogens. Dioxin exposure in utero may predispose female rodent offspring to mammary gland cancers. A study by Brown et al. [197] examined the effect of in utero TCDD exposure and the subsequent effect on rat mammary glands. The results showed TCDD-exposed offspring had increased terminal end buds at sexual maturity when compared with controls (terminal end buds differentiate to form lobules; lobules form the structures required for lactation). Terminal end buds are susceptible to carcinogens because of increased proliferation, as discussed above [197]. A study by Fenton et al. [198] was able to define the developmental window when dioxin exhibited these effects. TCDD exposure at gestation day 15, just after organogenesis, resulted in perturbation of mammary tissue development. However, TCDD exposure at gestation day 20 and postnatal day 5 did not result in any alteration of mammary tissue development. However, are these effects observed in rodents pertinent to environmentally relevant exposure levels of xenoestrogens?

Markey et al. [199] demonstrated that in utero exposure to environmentally relevant levels of bisphenol A resulted in perturbed mammary tissue development similar to that found following in utero TCDD exposure. The exposed mice had increased terminal ducts and terminal end buds when compared with controls, which predispose the mice to mammary gland cancers later in their adult life. The mice used were CD-1 mice, which are a strain that demonstrates particular resistance to the effects of oestradiol [199].
An alternative theory to the somatic mutation theory (SMT) is the tissue organization field theory (TOFT). In its earliest form, the TOFT was originally known as the morphogenetic field concept, which became the basic model of embryology. Soto & Sonnenschein [200,201] reinterpreted the theory, which is now known as TOFT.

The SMT, proposed by Boveri in 1914 [202], assumes that the default state of cells is quiescence and carcinogenesis occurs at the cellular level. The assumption that the default state of cells is quiescence probably arose from the fact that historically it was difficult to propagate metazoan cells in vitro in defined media; this may have led researchers to look for positive control factors (growth factors) to stimulate the cells [201,203]. The SMT may have been originally favoured by researchers because a large number of carcinogens were also found to be mutagens [201]. In addition, tumour-causing viruses were able to transform healthy cells and the subsequent discovery of over 100 oncogenes (gain of function mutations, homologous to human genes) and 30 tumour suppressor genes seemed to be consistent with the SMT [201,203]. Researchers thought they could integrate all these phenomena into one unifying theory [201]. Fifty per cent of carcinogens do not show mutagenicity in the Ames test (*Escherichia coli*) [204,205]. For example, the environmental pollutant TCDD, an extremely potent carcinogen, is not mutagenic [204,206]. A recent review by Soto & Sonnenschein [201] addresses their perceived inconsistencies and difficulties with the SMT.

Conversely, the TOFT is built on the assumption that the default state of cells is proliferative and that carcinogenesis occurs at the tissue level of biological organization. Thus, environmental damage to the tissue milieu in which cells exist may cause them to start dividing again. According to this hypothesis, it is not the cells that are damaged, but there is a disruption of the environment that normally constrains them, which renders them ‘malignant’ [200].

A point argued by researchers is that cancer cells have many mutations in oncogenes and tumour suppressor genes and some also have chromosomal aberrations. In a review by Prehn [204], the role of mutations in the new cancer paradigm (TOFT) is discussed. Prehn postulates that mutations are not responsible for the neoplastic phenotype of a cancer cell; rather the mutations are a consequence of the neoplastic phenotype and not the cause. Prehn’s interpretation of the TOFT includes four main premises:

- Cancer is initiated by a loss of gene function.
- DNA repair does not occur or is slow among silenced genes.
- Mutations will eventually ‘hard wire’ the silenced genes.
- The loss of expression among the genes that suppress developmental genes is seldom caused by mutation.

The main objection to this paradigm is that cancer cells may be clonally derived from a single cell. Prehn argues that the epigenetic adaptive changes will range within a tissue. Prehn states:

The new paradigm suggests that cancer supposedly originates via adaptive epigenetic changes within a tissue; however, the arises of focal papillomas suggests that the adaptive changes are not uniformly great among all the cells of that tissue. Thus, some clones may achieve a competitive advantage (based upon epigenetically-induced differential gene expression) and this competitive advantage might eventually and erroneously simulate an origin from a single cell.
A full discussion of Prehn’s review is beyond the scope of this text. In an editorial by Soto & Sonnenschein [207], the authors ask the question ‘are times a changing in carcinogenesis?’

The TOFT proposes that carcinogens perturb stroma–epithelial interactions, but thus far the actual target of carcinogens has remained hard to pin down. However, Maffini et al. [208] developed a rat mammary tissue recombination model, which encompassed previous attempts to provide a synthetic model that could test both theoretical approaches. The model provided a method for the stroma and epithelium to be exclusively exposed to the known chemical carcinogen N-nitrosomethylurea (NMU).

The model involved the surgical removal of mammary epithelium from mammary gland fat pads, and the experimental design would determine the primary target of NMU: either the epithelium or the stroma. Rats were divided into six groups: groups 1–4 had cleared fat pads, groups 5–6 were positive and negative control groups. At 52 days, groups 1 and 2 were exposed to 50 mg kg\(^{-1}\) body weight NMU in 0.85 g l\(^{-1}\) NaCl solution, groups 3 and 4 were exposed to vehicle (0.85 g l\(^{-1}\) NaCl solution). After a period of 5 days, 50,000 mammary epithelium cells were injected into the fat pads. Groups 1 and 4 received cells treated with the vehicle, groups 2 and 3 were injected with NMU-treated cells. The positive control animals were treated with NMU; group 6 animals were treated with vehicle alone to act as a negative control and the control for spontaneous tumours and to show the normal mammary gland architecture.

The results showed that phenotypically normal ducts developed from cultured mammary epithelium cells. Only animal groups that had their stroma exposed to NMU developed neoplasms whether or not the transplanted cells were exposed to NMU; 10 from 13 animals in group 1 and six from eight animals in group 2 developed neoplastic lesions. There was 100% incidence in the positive control group. The animals that were only exposed to vehicle whether or not the transplanted mammary epithelium cells were exposed to NMU developed no neoplasms. The negative control group (group 5) also developed no neoplasms.

Histopathological examination of the tumours in groups 1, 2 and 5 showed that all the tumours were epithelial in origin. The analysis also showed that the tissue-recombined mammary glands of rats that did not develop neoplastic lesions, whether or not the cells were NMU treated, appeared similar to a normal rat mammary gland. The authors also challenged the hypothesis that NMU-induced point mutations in codon 12 of the HA-ras-1 gene results in carcinogenesis. HA-ras-1 gene mutations were not found in all NMU-induced tumours and the mutation was also found in the mammary glands of animals that were not exposed to NMU.

The results of this experiment suggest that in NMU-induced mammary carcinogens, the stroma is the target. In addition, the findings challenge the theory that mammary cancers are initiated by carcinogens that cause mutations in the DNA of epithelial cells. The authors suggest that more research should be directed at the roles of the stroma components and the extracellular matrix in rat mammary carcinogenesis. Also, more efforts should be directed at investigating the role of the stroma in tumour sites other than the mammary gland [208].

**Prostate cancer**

**Prostate cancer incidence**

Worldwide prostate cancer is the third most commonly diagnosed cancer. However, in developed countries, prostate cancer is the most common cancer. There is geographical
variation in prostate cancer incidence, with the highest rates found in industrialized
developed countries [1,15,209,210]. However, there is also some variation in incidence
rates within developed countries [1,211]. The lowest rates are found in Asia, particularly
China and Japan [1,212]. In the USA, the incidence rate is approximately 137 per $10^5$
year$^{-1}$, whereas in China the incidence rate is approximately 1.9 per $10^5$ year$^{-1}$ [213]. In
the USA in 2003, an estimated 220,900 men were diagnosed with prostate cancer [214]. In
the UK, prostate cancer is the most common malignancy and the incidence has risen
consistently year on year [7,215]. The increased incidence rates in one study were
described as striking [216]. In the UK, in the 10 years between 1989 and 1997, prostate
cancer incidence increased by 38% (see Figure 3) [7]. Figure 9 shows the trend for the
number of cases and the age-standardized incidence rate for prostate cancer in England and
Wales, 1971–1999 [15]. The incidence trend shown in Figure 9 is mirrored in the rest of
the developed world [1].

The marked increases in incidence may in part be due to the diagnosis of latent cancers
in men who are asymptomatic, by screening for prostate-specific antigen or from
histological examination following prostatectomy operations [1,209,211,217–219].
However, a rising incidence is observed in countries and regions where the effects of
screening may not influence the incidence rate [1,210,216]. In addition, in countries where
prostate cancer incidence rates have been historically low, increases in incidence rates can
now be observed [1]. The analysis of data in some studies suggests that younger people
showed a higher rise in incidence than the elderly [208,216,219].

Factors involved in prostate cancer aetiology
The factors involved in prostate cancer aetiology are poorly understood, but genetic
susceptibility and environmental factors are thought to play a major role. The risk of

![Figure 9. Trend for incidence of prostate cancer in England and Wales, 1971–1999 (all ages). Data taken from [15].](image)
prostate cancer increases two-fold for men with first-degree relatives affected by prostate cancer [209,220]. Mutations in the genes BRCA1 and BRCA2 are associated with an increased risk, but these mutations are rare. Gene linkage studies to find other genes that may be involved in increased risk have been both promising and confusing [220]. Because of the geographical variation in incidence and differences in diet between countries with high and low prostate cancer incidence rates, products such as meat, fish, milk, dairy products and eggs have been postulated in prostate cancer aetiology [1,221–224]. Studies on the correlation of dietary factors and increased prostate cancer risk are conflicting.

A study by Homma and colleagues [221] demonstrated that dietary cholesterol increased oxidative stress and ultimately carcinogenesis in the prostate in rats. In the Netherlands prospective cohort study, no association was found for meat, fish, and dairy products (except milk), protein and calcium intake and an increased risk of prostate cancer. However, a positive correlation was found for milk and cured meats, which was in concordance with similar studies [222,225–227]. Li and colleagues [226] demonstrated that the consumption of milk increases the risk of developing prostate cancer in rats and Qin and colleagues [222] put forward the hypothesis that oestrogens in milk may be a factor in the positive correlation between milk consumption and increased prostate cancer risk.

Steroid hormones such as testosterone and oestrogen can induce prostate cancer in vivo and in vitro. However, circulating androgen and oestrogen levels in epidemiological studies have produced conflicting results. A nested case–control study by Stattin et al. [228] showed no association between high levels of circulating androgens and an increased risk of prostate cancer. A similar result in another nested case–control study was found by Chen et al. [229]. However, Chen et al. postulated that intraprostatic androgen activity may increase the risk of prostate cancer. To obtain more reliable information concerning any possible role of androgens in the aetiology, samples may have to be taken prospectively, preferably at puberty [209].

Environmental contaminants as factors in prostate cancer aetiology

Environmental pollutants with endocrine-disrupting properties have also been postulated as possible factors in prostate cancer aetiology. As discussed in previous sections, pesticides have been shown to have endocrine-disrupting properties. Moreover, studies concerning occupational exposure to pesticides have shown an association with an increased risk of prostate cancer. Data taken from a multisite case–control study in five rural areas in Italy showed that workers involved in agriculture, especially farmers, had an increased risk of prostate cancer. Workers involved in the food, tobacco and chemical industries also showed an increased risk [230]. Farmers were especially vulnerable to organochlorine pesticides. Another study linking occupation and prostate cancer risk by Sharma-Wagner et al. [231] suggested that there is a significant excess risk for men in agriculture-related industries, and for farming in particular there was a significantly elevated risk for prostate cancer. Men working in other industries such as soap and perfume manufacture, and leather processing, had a significantly excess risk of prostate cancer.

A meta-analysis of 22 studies concerning occupational exposure to pesticides and prostate cancer found that the meta-rate ratio estimate of relative risk from 22 studies was 1.13. The increased risk of prostate cancer following occupation exposure, including farmers, was in agreement with three, previously published, meta-rate ratios [23]. A study cohort of 20,025 men who held a licence for pesticide application in Sweden had a significantly increased risk of prostate cancer [232].
A retrospective study by Potti et al. [233] concentrated on the effect of pesticides on aggressive prostate cancer incidence in males younger than 50 years with prostate adenocarcinoma from rural/farming communities in the USA. An exposure index was formulated and a cut-off point of 2400 hours was considered as heavy exposure. The study showed preliminary evidence that pesticide exposure may lead to the early development of prostate cancer and possibly to an aggressive form. The pesticide-exposed patients had a mean survival time of 11.3 months, while unexposed patients had a mean survival of 20.1 months. The authors are now studying the effects of specific pesticide components in PC-3 and LNCaP cells to evaluate for the over-expression of biomarkers such as vascular endothelial growth factor and urokinase plasminogen activator receptor. The authors also concluded that larger epidemiological studies should be carried out to determine which pesticides and pesticide components may be associated with the early progression of aggressive prostate cancer in young (≤50 years) males [233].

Three different in vitro and in vivo experimental techniques carried out in a study by Ralph et al. [234] showed that HCB weakly agonized androgen action: low levels of HCB enhanced androgen action but high levels suppressed androgen action. PC3 cells transfected with an androgen-responsive reporter gene (firefly luciferase reporter gene) in the presence of a low dose level of HCB (0.5–5 nM) showed increased transcription of the reporter gene. However, high levels of HCB (>10 μM) resulted in suppression of the reporter gene. A similar trend was observed for three different reporter genes (ERE-luc, ARR3-luc, and PSA-luc). Another experiment determined that HCB is not an androgen receptor ligand. A further in vivo experiment, in which transgenic mice with a prostate-specific, androgen-responsive promoter upstream of a chloramphenicol acetyl transferase (CAT) reporter gene were prenatally exposed to HCB, showed HCB-modulated androgen action. Following low-dose exposure to HCB in 4-week-old male mice, the proportion of dilated prostate acini, a marker of sexual maturity, was increased, suggesting enhancement of androgen action. In high-dose HCB mice, androgen action was suppressed. In the 8-week-old mice, CAT activity and prostate weight were significantly reduced with medium and high doses of HCB, suggesting the suppression of androgen activity [234].

These latter results concur with a study carried out by vom Saal et al. [121], which also showed that endocrine-disrupting chemicals can exert their effects at environmental exposure levels. They found that low doses of DES (0.02, 0.2 and 2.0 ng g\(^{-1}\) day\(^{-1}\)) resulted in a significant increase in adult prostate weight and an increase in the number of androgen receptors, when compared with control mice. However, high doses of DES (200 ng g\(^{-1}\) day\(^{-1}\)) had the opposite effect: prostate weight was significantly lower than control mice and significantly lower than low-dose treated mice [121].

Tessier & Matsumura [235] have shown that in human prostate cancer cell lines LNCaP and PC-3, erbB-2 kinase, an oncogene that is often over-expressed or amplified in prostate cancer, was activated by the pesticides: \(\beta\)-HCH, \(\text{o,p'-DDT}\) and heptachlor epoxide (organochlorines), trans-permethrin (insecticide), chlorothalonil (fungicide). \(\text{o,p'-DDT}\) also causes cellular proliferation of the androgen-dependent LNCaP line. However, no proliferation was observed in the androgen-independent PC-3 line [235]. The proliferation induced by DDT could not be blocked using anti-androgens, indicating that the action of DDT is not via the androgen receptor, a similar finding to a previous experiment with HCB [234,235]. Tessier & Matsumura concluded that their results showed a putative mechanism by which pesticides may be involved in hormonal carcinogenesis [235].
A pilot case–control study by Ritchie et al. [236] investigated the possible relationship between organochlorine pesticides and PCBs with prostate cancer. Levels of 30 PCBs and 18 organochlorine pesticides were measured. The organochlorines dieldrin, p,p′-DDE, trans-nonachlor, oxychlordane, heptachlor epoxide, and PCBs 153 and 180 were detected in at least 20% of all the participants in the study. Oxychlordane and PCB 180 were associated with an increased risk of prostate cancer. The authors concluded that long-term, low-dose exposure to specific organochlorine pesticides and PCBs in the general population may lead to an increased risk of prostate cancer [236]. A study by Alavanja et al. [237] found a significantly elevated risk for prostate cancer in men over 50 years who had occupational exposure to the halogenated fumigant methyl bromide. Exposure to organochlorine pesticides also showed an elevated risk. In addition, other pesticide types showed a significantly increased risk of prostate cancer among pesticide applicators with a family history of prostate cancer but not among pesticide applicators with no family history; suggesting family history–pesticide interactions [237].

The results from a study by Janssens et al. [238] did not find an association with prostate cancer mortality in areas where pesticides were used abundantly, for example, on fruit farms. Fruit production needs the greatest amounts of fungicides, acaricides, insecticides and herbicides, in total up to 25 kg hectare\(^{-1}\) year\(^{-1}\). However, higher prostate cancer mortality was found in traditional potato growing areas. The authors suggested that this may be due to a long-standing effect of pesticides now currently banned, such as DDT [238].

The studies discussed above suggest that occupational exposure to organochlorines is an important factor in the aetiology of prostate cancer. In addition, the evidence provided by in vitro studies suggests that exposure to environmentally relevant levels of specific organochlorines and endocrine-disrupting chemicals could be a major factor in increasing prostate cancer incidence.

**Testicular cancer**

**Testicular cancer incidence**

Testicular cancer is the most common malignancy in 20–34-year-old men, and is increasing in incidence worldwide. The majority of this increase is in developed industrialized countries, i.e. North America, Europe, Oceania and Japan [239]. However, Denmark has reported a decrease in incidence [150,240]. The worldwide rate of testicular cancer has doubled in the last 40 years. There seem to be geographical differences in the incidence of testicular cancer; ethnicity also plays a role in the differences in incidence observed between different countries and within differing regions of countries [239,241]. This suggests that environmental influences could be involved in the aetiology. However, the differences in incidence observed between differing ethnic groups suggest that genetics is also involved in testicular cancer aetiology. In the UK, the familial risk accounts for approximately 2% of the overall incidence. A mutation in chromosome Xq27 has been found to be associated with the familial risk. Brothers of affected men have a six to 10 times risk of developing testicular cancer [242].

In the UK, 80% of testicular cancer incidence affects men aged under 45 years. Considering 10-year age groups, testicular cancer has increased in all age groups from 20 to 59 years but not in the over 60s. Overall, incidence was 5.4 per 10\(^5\) in 1997 compared with 2.9 per 10\(^5\) in 1971 [15]. A study by dos-Santos Silva and colleagues [243] compared
incidence rates in children and young adults in England and Wales. The incidence rate overall rose by 3.4% between 1965 and 1990. The incidence rate in under 15 year olds rose by 1.3% from 1962 to 1995. This rise in incidence in under 15 year olds was paralleled by a rise in young adults. Both trends are in the same direction, suggesting a common aetiology, possibly prenatal [237]. Figure 10 shows the trend for the incidence of testicular cancer for England and Wales (all ages), 1971–1999 [15].

Occupational exposure to polychlorinated compounds has been shown to increase the risk for some cancers. Hardell et al. [244] examined occupation histories in a case–control study in Sweden and found a high risk of testicular cancer in people exposed to PVC; exposure to other types of plastics did not increase the risk. However, a further case–control study was carried out by Hardell et al. [245] and no association between PVC exposure and testicular cancer was found.

The average age of testicular cancer incidence is 25–30 years, suggesting that the exposure to carcinogens was in early life or even in utero. Pre-malignant germ cells that eventually give rise to testicular cancer are thought to originate during foetal life [150]. Swerdlow and colleagues [246] carried out a study on risk factors for testicular cancer in a case–control study in twins. They found an increased risk of testicular cancer in twins with longer limbs than their co-twin. A correlation between height and testicular cancer has also been observed in another study conducted by Rasmussen et al. [247]. The authors of these studies concluded that nutritional factors that affect growth before puberty may cause testicular cancer. The study by Swerdlow et al. [246] also reported an increased incidence of testicular cancer among twins with cryptorchidism.

Figure 10. Trend for incidence of testicular cancer in England and Wales, 1971–1999 (all ages). Data taken from [15].
Early life exposure to carcinogens and testicular cancer

There is a growing body of evidence to suggest that exposure to increased oestrogen levels in the prenatal period may be involved in the aetiology of cancer. In 1971, a now well-cited study by Herbst et al. [248] demonstrated that women given the potent oestrogen DES to prevent spontaneous abortion gave birth to female offspring who went on to develop clear cell adenoma of the vagina. If testicular cancer is considered: increased exposure to maternal oestrogen levels has been shown to be associated with testicular cancer [249,250]. Counter-intuitively, one study found that mothers smoking 12 cigarettes a day decreased the risk of testicular cancer. In addition, the disorders cryptorchidism, testicular cancer, low sperm count and hypospadias may be a syndrome of disorders known as TDS, which have a common aetiology during foetal life and may be a consequence of increased oestrogen exposure [82,150,251,252]. Each of these disorders is a factor for any of the other disorders in the syndrome. Therefore, a factor implicated in the aetiology of one of these disorders is also a factor in the aetiology of one of the other disorders.

The ‘oestrogen hypothesis’

A review by Sharpe [150], which examined data pertinent to his ‘oestrogen hypothesis’, cites a case–control study by Dieckmann et al. [253] that failed to find any evidence to back up the hypothesis that maternal exposure to excess exogenous oestrogen in males was a risk factor for germ cell cancers. Stroshnitter et al. [249] examined DES exposure in utero and after the first 16 years of follow-up obtained an uncertain result with respect to testicular cancer, but they concluded that for males, DES exposure in utero is not a factor in the aetiology of other cancers. Men exposed to DES in utero did have an increased relative risk of testicular cancer compared with controls, but the authors could not rule out a chance finding. However, Weir et al. [250] found an elevated risk between exogenous oestrogen exposure in utero and testicular cancer.

Oestrogens may induce male reproductive disorders, including testicular cancer, via many different mechanisms, for example, androgen suppression. Sharpe [150] cites a study by Haavisto et al. [114] in which potent oestrogens such as DES suppress androgen production in foetal rats, and a study by Williams et al. [115] that showed that DES and ethinyl oestradiol exposure leads to reduced testosterone levels in neonatal rats. However, the same study showed that exposure to low potency environmental oestrogens, octylphenol and bisphenol A, did not produce the same results. DES suppresses Leydig cell function, which results in a significant reduction in testosterone levels in foetal testis and blood, which is dose dependent. Williams et al. [115] demonstrated that treatment with high, but not low, doses of potent oestrogens such as DES and ethinyl oestradiol induces widespread structural and cellular abnormalities of the testis and reproductive tract before puberty. Haavisto et al. [114] also showed that DES doses of 100 μg kg⁻¹ day⁻¹ administered to pregnant rats resulted in the suppression of testosterone in the testis by as much as 70%. Sharpe points out that similar doses of DES were given to pregnant women between 1950 and 1970 [115]. Haavisto et al. [114] also showed that dioxin causes dose-dependent suppression of foetal testosterone.

Could exposure to environmental pollutants with oestrogenic activity increase the risk of TDS and testicular cancer? Hardell & Eriksson [254] carried out a case–control study in which they examined levels of the sum of 38 PCBs, DDE, HCB and chlordane, in cases with testicular cancer and age-matched controls. In addition, the mothers of cases and controls were also examined. The results showed that only one type of chlordane,
cis-nonachlordane, was significantly raised in cases. However, compared with control mothers, the mothers of cases were found to have significantly raised levels of total PCBs, HCB, cis-nonachlordane, and the sum of chlordanes. The authors pointed out that persistent organic pollutant levels are decreasing in the population and the highest concentrations were found in the early 1970s. The median age of the cases was 30 years. Therefore, most of them were born during the period with high concentration in the population [254].

Environmentally relevant levels of xenoestrogens and testicular cancer

Sharpe addresses environmental oestrogens as factors in the aetiology of testicular cancer. Most environmental xenoestrogens, when assayed for oestrogenic activity, are thought to be weak. He concludes that the weak oestrogenic activity of most environmental oestrogens is probably not important in cancer aetiology [150]. However, as discussed earlier, there are studies that show endocrine disruption and in utero effect with substances at low levels and low oestrogenicity. Hormones involved in organogenesis act at part per trillion levels and hormone-disrupting chemicals are found in similar serum concentrations [65].

A good example of a study showing the effect of environmentally relevant levels of bisphenol A on CD-1 mice was carried out by Markey and colleagues [199]. Although the study examined the effect of bisphenol A on developing mammary tissue and not the developing male reproductive tract, the study produced evidence of adverse effects from oestrogen exposure at background environmental levels. Bisphenol A is an environmental oestrogen used in the manufacture of polycarbonate plastics and epoxy resins, which are used in the production of infants’ milk bottles, reusable food containers and the interior coating of food tin cans and many other widely used products. The study demonstrated that in utero exposure to environmentally relevant levels of bisphenol A results in perturbed mammary tissue development. The exposed mice had increased terminal ducts and terminal end buds when compared with controls, which predispose the mice to mammary gland cancers later in their adult life [199]. The CD-1 mice were used because they have intrinsic oestrogen resistance.

The major endocrine disrupter Vinclozolin (fungicide) has been shown to have an in utero effect resulting in maldescent of the testis in neonatal rats [113]. In addition, the phthalate ester, mono-n-butyl phthalate (MBP) has a dose-dependent effect on in utero and postnatal testis descent in rats. High doses of MBP (1.0 and 0.5 g kg\(^{-1}\) day\(^{-1}\)) inhibit the transabdominal descent of the testis, which the authors concluded is due to the oestrogenic activity of MBP. However, low doses of MBP (0.25 g kg\(^{-1}\) day\(^{-1}\)) inhibit inguinoscrotal testicular descent in postnatal rats, which may be due to the anti-androgen affect of MBP at low doses [96].

There are conflicting studies regarding the effects of xenoestrogens with low oestrogenic activity on animals, but if these compounds are not directly involved in the aetiology of testicular cancer, there is growing evidence that they may be indirectly involved. High levels of endogenous oestrogen are a known cause of testicular cancer [241]. If high levels of endogenous oestrogens cross the placenta, adverse effects on the foetus may be observed. The enzyme oestrogen sulphotransferase (SULTE1E1) is responsible for the inactivation and excretion of oestradiol. However, if this enzyme is inactivated, increased levels of oestrogen can reach the foetus. Low levels of PCBs have been shown to suppress SULTE1E1 activity. Hydroxylated PCBs inhibit the enzyme and the level of inhibition depends on where the hydroxyl substations are on the phenyl ring. Some congeners of PCBs have a greater affinity for SULTE1E1 than its natural substrate. A PCB congener
found to be one of the most potent inhibitors of SULT1E1 is also found to be one of the most abundant in the blood and tissues of humans and animals. Inhibition of this enzyme may increase local levels of oestrogen in oestrogen-sensitive tissues, for example the testis and mammary glands [101]. Further studies by Kester et al. [100] revealed that other organochlorines, in addition to PCBs-OH, also have a potent inhibitory effect at very low levels. The concentrations causing 50% inhibition (IC\textsubscript{50} values) were in the low or even subnanomolar range. The potent inhibitors 2-hydroxy-3,7,8-trichlorodibenzo-p-dioxin, 2-hydroxy-1,3,7,8-tetrachlorodibenzo-p-dioxin, 3-hydroxy-2,4,7,8-tetrachlorodibenzofuran, and 3-hydroxy-2,4,7,8,9-pentachlorodibenzofuran, with IC\textsubscript{50} values of 34, 4.1, 1.4 and 0.18 nm, respectively, have been identified in mammals [100].

Environmental influences in childhood cancer aetiology

Childhood cancer incidence and common childhood tumour sites

A report released in 2003 by the US Environmental Protection Agency shows increasing childhood cancer incidence [64]. Cancer in childhood is quite rare when compared with adults. However, in the USA, only accidents and injuries cause more deaths in children between 1 and 19 years of age (see Figure 11) [64]. Similar trends for childhood cancer can be observed in the UK and the rest of the developing world [12,13,64,255] (see Figure 12a).

![Cancer incidence and mortality trends for children under 20 years in the USA (1974–1998). Data taken from [64].](image-url)
In the USA, the childhood cancer incidence rate for all cancer sites has increased from 128 cases per $10^6$ in 1975 to 161 cases per $10^6$ children in 1998 (see Figure 11) [64]. However, the mortality rate is decreasing: the mortality rate has fallen from 51 deaths to 28 deaths per $10^6$ children. If specific cancer sites are considered, the incidence rates of acute lymphoblastic leukaemia, central nervous system cancer, NHL, thyroid cancer, malignant

![Figure 12. Trend for age-standardized incidence rate (European) for all malignancies in children under 20 years in England and Wales, 1971–1999, for (a) males and (b) females. Data taken from [64].](image-url)
melanoma, germ cell tumours, soft tissue carcinomas, malignant bone tumours, neuroblastomas, Wilms’ tumours and hepatoblastomas have increased. However, from available data, only acute myeloid leukaemia and Hodgkin’s lymphoma have had decreased incidence rates since 1975 [64].

In the UK, the six most common childhood cancers are: leukaemia, brain and spinal cord cancers, lymphomas, neuroblastomas and renal cancer. However, there is also a marked upward trend in the incidence of testicular cancer in children [13]. Figure 12a, b shows the increasing trend for the age-standardized incidence rate for childhood cancer (all malignancies) in England and Wales [15]. Cancer incidence in children in North West England is rising and the increase is real; it is not a consequence of improved diagnosis or reporting [14]. A recent analysis of cancer incidence data for England shows that the overall incidence among teenagers, adolescents and young adults is rising. The biggest increase is among 20–24 year olds, predominantly in lymphoma, melanoma and germ cell tumours, including testicular germ cell tumours. Cancer is the leading cause of death apart from accidents in England among 13–24 year olds. Between 1979 and 2000 the overall rate of cancer incidence in 13–24 year olds rose from 15.4 to 19.8 per 10^5; a total increase of 29% and an average increase of 1.2% year^{-1} [256,257].

- Leukaemia accounts for around 33% of all childhood cancers; acute lymphoblastic leukaemia is the main form in children; around four out of five leukaemia cases in children is acute lymphoblastic leukaemia. Leukaemia in children occurs mainly at 2–3 years of age.
- Brain and spinal cord malignancies are the most common form of solid tumours in children. In England and Wales they are responsible for 25% of childhood cancers. Between 30 and 50% of childhood malignant brain tumours are astrocytomas. Childhood brain and spinal cancer incidence rose from 19 cases per 10^6 in 1971 to 26 cases per 10^6 in 1994, which was an increase of approximately 40%. Since 1971, the incidence rate has doubled in the 5–9 years age group.
- Lymphomas occur more frequently in older children aged 10–14 years.
- Soft tissue sarcomas are responsible for approximately 7% of malignant neoplasms in children. They are the fourth most common form of childhood cancer in England and Wales. The most common form in children is rhabdomyosarcoma.
- Neuroblastomas are embryonal tumours, which account for approximately 6% of cancers diagnosed in children in England and Wales. Three-quarters of cases occur in children aged under 4 years.
- The majority of renal cancers are Wilms’ tumours (nephroblastoma). They are most commonly diagnosed in children between the ages of 1 and 3 years [83,256].

Environmental factors involved in childhood cancer aetiology

Ionizing radiation is an established risk factor for childhood cancer, and leukaemia clusters around nuclear power stations have been investigated. Leukaemia clusters around the Sellafield reprocessing plant in the UK were investigated following public concern. Ionizing radiation was not thought by some to be the cause of the increased incidence in leukaemia. An infectious agent was postulated by Doll [58] as being responsible. Doll hypothesized that the infectious agent was brought into the local community by population mixing. The hypothesis of population mixing is based around the introduction of a wide variety of infectious agents into a previously unexposed, sparsely, populated area. Rapid population
influx into a rural area such as Sellafield, particularly by workers from urban backgrounds across the North West of England who may have been exposed to many infectious agents, was proposed by Doll to have caused the leukaemia cluster. There was a similar finding for a cluster around the nuclear power plant in La Hague, France [258]. Nonetheless, the viral aetiology hypothesis remains controversial.

Cancer treatments in childhood, for example, chemotherapeutic agents, can be risk factors for re-occurrences of primary tumours at different sites later in life [83]. A study suggesting that breast-feeding may offer protection against childhood cancer, especially acute lymphocytic leukaemia [169], has been challenged by Lancashire & Sorahan, who concluded that there is no evidence to support the protective hypothesis [259].

It is difficult to find a specific causal link between environmental pollutant exposure and cancer development. Many factors may be involved in the aetiology of childhood cancers. As discussed above, population mixing and infectious agents have been hypothesized for leukaemias and some brain tumours [58,61,258,260,261]. Space–time clustering acute lymphoblastic leukaemia incidence analyses by McNally et al. [262] suggested that an in utero infection may be a factor in acute lymphoblastic leukaemia aetiology.

Environmental exposure to persistent organic pollutants such as PCBs, pesticides and other endocrine disrupters, has been studied to a lesser extent in the case of children and more epidemiological studies are needed [83]. Childhood behaviour puts children at risk to high exposures: they crawl on the ground, they put their fingers in their mouths, and they inhale more air per unit body weight than adults. Children are potentially at risk of exposure to more than 85,000 synthetic chemical compounds, most of which have been developed since World War II [64].

Exposure to PCBs early in childhood has been shown to have neurological and immunological effects on children. A study on pre-school Dutch children suggested that perinatal exposure to PCBs and dioxin, probably from lactation, persists into childhood and has an adverse effect on infection susceptibility. Weisglas-Kuperus et al. [263] found that the effects of perinatal exposure on the immune system led to increased middle ear infections and other infectious diseases. Paradoxically, perinatal PCB exposure led to a decrease in allergy in this study and a study by ten-Tusscher et al. [264] that also found that perinatal background dioxin exposure led to persistently decreased thrombocytes, increased thrombopoietin, and increased CD4+ T-helper and increased CD45RA+ cell counts. In a recent review, human prenatal exposure to PCBs and their effect on neurodevelopment was studied. The authors found that the neonates had impaired reflexes and at 4 years of age deficits in cognitive skills were observed [265].

Could pesticide exposure be implicated in childhood cancer aetiology? A study by Rodvall et al. [22] in Sweden examined the cancer risk in offspring of male pesticide applicators in agriculture. The authors found no link to childhood cancer. A similar study in the USA and Canada also came to the conclusion that parental pesticide exposure was not an important factor in the aetiology of childhood brain cancers [266]. A study examining the critical windows of exposure of household pesticides, and the subsequent risk of childhood leukaemia conducted by Ma et al. [267], suggested that exposure to these substances increased the risk of childhood leukaemia. The risk of childhood leukaemia was determined by the period (pregnancy, year 1, year 2, and year 3) when exposure occurred. The highest risk was during pregnancy and the lowest was at year 3. The risk of leukaemia was associated with indoor pesticides but not outdoor household pesticides [267].

The study by Ma et al. [267] showed that exposure to pesticides during pregnancy and the first year of life had the principal adverse affect. Pre- and perinatal exposure to
environmental pollutants is obviously an important factor in the aetiology of perturbed development. Could prenatal or perinatal exposure to pesticides and other endocrine-disrupting chemicals lead to cancer development in childhood?

**Pre- and perinatal exposure to environmental carcinogens**

*The intrauterine environment is exquisitely sensitive to ambient hormone level fluctuations*

Evidence suggests that developing children are vulnerable to environmental exposures, from conception to adolescence. Exposures to ionizing radiation and DES *in utero* are undisputed environmental factors involved in the aetiology of cancer [66,248,265,267–269]. There are critical sensitive periods during organogenesis and environmental exposure to chemicals may have differing or no adverse effects on a developing foetus, depending on the precise time of exposure. A specific developmental process occurs during a specific period of time. Thus, a chemical may have an adverse effect at one point in time, but before or after that point in time the chemical may have no effects at all [270–272].

The intrauterine environment has been shown to be exquisitely sensitive to ambient hormone fluctuations at a few parts per trillion; this is approximately the same concentration that dioxins and other organochlorines are found in serum. In a classic study involving incubating mice pups, differences of only 30 ppt in the ambient uterine level of oestrogens between the pups had effects on their subsequent behaviour as adults. Females incubated between two males were more aggressive than their sisters [273]. A study investigating *in utero* exposure to PCBs from eating fish from Lake Michigan, USA, found that prenatal exposure to PCBs was associated with lower full-scale and verbal IQ scores. In addition, children with the highest PCB exposures were three times as likely to have low average IQ scores and twice as likely to be 2 years behind in reading comprehension. These results suggested that the developing foetal brain is extremely sensitive to PCBs. The authors of the study concluded that *in utero* exposure to PCBs in concentrations that are slightly higher than the general population can result in long-term consequences for intellectual function [274].

The high rates of cell proliferation and differentiation render the developing child’s cells susceptible to mutagenic and epigenetic alteration. The blood–brain barrier and the placenta act as barriers to potentially harmful substances. However, in the developing foetus, these protective barriers are not fully developed and can allow harmful substances to reach sensitive developing organs such as the brain [268,270]. *In utero* DNA damage resulting from environmental pollution has been shown to be associated with somatic gene mutation in newborns. The authors of this report state that their results provide a molecular link between transplacental exposure to pollutants and somatic mutation [66].

*Animal models of prenatal exposure to endocrine disrupters and carcinogenesis*

Human epidemiological and biological data are inconsistent, but the animal evidence of prenatal exposure to environmental carcinogens is abundant and has been reviewed extensively [82,106,116,268,271,275]. A review by Birnbaum & Fenton [275] concerning cancer and developmental exposure to endocrine disrupters explores suggested links in human and animal models. The authors cite studies in which links have been found between occupational prenatal exposure and, in some cases, preconceptional paternal exposures and cancer for hydrocarbons [276], solvents and paints [277], pesticides [278,279] and parental smoking [280].
Animal studies have suggested that in utero exposure to natural and synthetic oestrogens is associated with breast and vaginal cancers, and this association has also been demonstrated in humans [196,248,281]. There is some preliminary evidence that women exposed to DES in utero may have an increased risk of developing breast cancer later in life. The results of a cohort study showed an association between DES exposure in utero and an increased risk of breast cancer. The results were not statistically significant, but as the cohort was of mean age 43 years, the authors will be conducting a further follow-up [196].

As discussed in detail earlier, rodent studies have suggested that exposure to dioxin and other organochlorines in utero may predispose female offspring to breast cancer, as demonstrated by Brown and colleagues [197] and Fenton et al. [198] for TCDD, and Markey et al. [199] for bisphenol A.

A study by Emmen et al. [282] investigated whether inactivation of the insulin-like factor 3 gene (Insl3) by in utero DES exposure would result in cryptorchidism in male mice. Insl3 plays a role in transabdominal testicular descent, which involves the development of the gubernaculum. Histological examination of the mouse embryos showed differences in the position of the testis between treated and control mice. In treated mice the testes were always in a higher abdominal position than in the control mice. In addition, DES-treated mice showed an undifferentiated female-like gubernaculum. Further RNA analysis showed a 70% decrease in Insl3 mRNA compared with control mice. The Insl3 gene has been characterized in humans and in situ hybridization has shown Insl3 to be exclusively expressed in Leydig cells [282]. This study demonstrated the possible mechanism by which DES exposure in utero causes cryptorchidism. As discussed in a previous section, cryptorchidism is a factor in the aetiology of testicular cancer.

The hypothesis that early life exposure to environmental factors such as organochlorine endocrine disrupters may be involved in cancer aetiology is plausible. There is, however, a study that disagrees with this hypothesis. Hsieh et al. [283] reason that populations with high pregnancy oestrogen levels should have increased rates of testicular cancer. The study examined pregnancy oestrogen levels in two populations (Boston, USA and Shanghai, China) with different testicular cancer rates. Women in Boston had lower oestrogen levels than the women in Shanghai, but the testicular cancer rate was higher in Boston than Shanghai.

Data obtained from animal studies concerning environmental exposures in utero and the subsequent development of cancer are extensive. However, animal evidence must be treated with caution because results from animal experiments are not automatically applicable to humans. An example is prenatal rat exposure to saccharin, which is an artificial sweetener. Prenatal exposure results in an increased incidence rate of bladder cancer when compared with adult rat exposure. However, following a comprehensive review of studies regarding saccharin exposure to rats, mice, hamsters and humans, saccharin was considered to be safe [281,284,285].

Reduction in female body burden of organochlorines: implications for the foetus and infant; placental and lactation transfer of organochlorines to foetus and infant

Although organochlorines such as dioxins and PCBs bioaccumulate in adipose tissue, females can reduce their body burden transplacentally and via lactation [130,133,135]. It has recently been shown that HCB also exhibits transplacental transfer [132]. The foetus gets a huge dose compared with the dose that adults receive from background levels. Consequently, most testing on adult animals may not give results that apply to the foetus and infant. One study indicated that the body burden of organochlorines in women can
potentially reduce by as much as 69% over a 30 month period. Dioxins, dibenzofurans, PCBs, DDE, and HCB were measured in blood and milk samples. Dioxin levels in the milk samples fell from 309 to 173 ppt and dibenzofuran levels fell from 21 to 9 ppt. The authors calculated that the mother’s body burden of dioxin reduced from 310 to 96 ng dioxin toxic equivalents, approximately 69%. It was calculated that the twins born to the mother received the equivalent of 115 ng dioxin each from breast-feeding [135]. A study on urban foxes demonstrated similar results to the study above. The authors concluded that urban foxes possess the requirements to enable assessment of the toxic health hazards in the local environment [286].

A study on school-aged children (7 years) suggested that those who were breast-fed had a higher body burden of organochlorines than those who were bottle-fed. The study found a strong dose-dependent relationship between the length of time the infants were breast-fed and the concentration of all the organochlorines measured (DDE, HCB, \( \beta \)-HCH, and the sum of PCBs including the congeners 101, 118, 138, 153, 170, 180, 183, and 187). There was a doubling of organochlorine whole blood concentration in children who were breast-fed for a period greater than 12 weeks compared with bottle-fed children [133]. However, another study revealed that prenatal uptake of PCBs and HCB has declined by 75 and 95%, respectively, over the last 15 years [287].

In utero exposure to PCBs and HCB from tobacco smoke

The PCB and HCB burden is significantly increased in human neonates with parents who smoke, when compared with passive smoking mothers and non-smoking families. In addition, a transplacental tobacco carcinogen (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) has been found in the urine of neonates. PCBs and HCB have been shown to have a co-carcinogenic effect with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in mice [288]. The uptake of PCBs and HCB by neonates from tobacco smoke with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone could be a risk factor for childhood cancers and the authors concluded that further studies are required to investigate the possible risks associated with parental smoking, with special consideration of the tumour-promoting properties of PCB and HCB [289].

**Immune system cancers**

*Characteristics of immune system cancers*

Cancers of the immune system include lymphomas, leukaemias and multiple myeloma. Lymphomas typically arise from lymphoid tissue and comprise two major groups: Hodgkin’s lymphoma and NHL. NHL is a collection of malignancies and Hodgkin’s lymphoma is distinguished from NHL by the presence of large malignant cells called Reed–Sternberg cells. Leukaemias are tumours arising from a group of white blood cell types called leukocytes. Multiple myeloma, which is the least common of the immune cancers, is a malignancy of the plasma cell characterized by migration and localization to the bone marrow.

*NHL and multiple myeloma incidence*

NHL has increased rapidly in the majority of developed countries over the past few decades. The highest incidence rates for NHL are found in the USA and Australia for both
males and females. The lowest incidence of NHL is found in India and China (see Figure 13a, b) [256]. The incidence rate of NHL has started to fall in the USA, Sweden, Finland and Denmark, but not in Norway or the UK [15,254]. A possible reason for this

Figure 13. International age-standardized incidence for (a) males and (b) females. Adapted from [253] (Grown copyright material is reproduced with the permission of the Controller of HMSO and the Queen's Printer for Scotland).
decline is discussed in detail below. Multiple myeloma is also increasing and childhood leukaemias also show increasing incidence in the USA [64] and the UK [256]. Figure 14 shows the trend for the incidence of NHL in England and Wales, 1971–1999 [15]. The incidence rate of NHL in England and Wales is comparable to the rest of Western Europe [256].

Environmental factors involved in NHL aetiology, particularly pesticides, dioxins and dibenzofurans

The factors involved in the aetiology of NHL include HIV and Epstein–Barr virus (EBV) infection, immunosuppression by drugs (e.g. cyclosporin A), family history, immunodeficiency disorders, and occupational exposure to chemicals, particularly pesticides [51,69,70,256,290–297]. EBV is a human herpes virus and infection with the virus is a major risk factor for NHL in Africa and other developing countries. The virus is associated with Burkitt’s lymphoma (a subgroup of NHL) and lymphomas arising from severe immunosuppression. Table II shows organochlorines that have been shown to cause immune cancers in laboratory animals [298].

Occupational exposure to pesticides has been shown to increase the risk of NHL, particularly among farmers, pesticide applicators and other agricultural workers. In the Agricultural Health Study, pesticide exposure (alachlor) for applicators in Iowa and North Carolina, USA, was found to be associated with an increased risk for all lymphohaematopoietic cancers among applicators, although the risk for NHL was significantly lower than expected. There was a significant increasing trend associated with lifetime exposure-days and intensity-weighted exposure-days. In the highest exposure category, a marked increasing risk was found for leukaemia and multiple myeloma [20].

![Figure 14. Trend for incidence of non-Hodgkin's lymphoma (C82-85) in England and Wales, 1971–1999 (all ages). Data taken from [15].](image-url)
In Nebraska, USA, which is a rural, agricultural area, the incidence of an aggressive subtype of NHL has increased two-fold. A population-based case–control study was carried out to investigate any possible association between agricultural exposure and increased risk of NHL. The results showed that an increased risk of 50% was found with 2,4-dichlorophenoxy-acetic acid (2,4-D). In addition, personal exposure to 2,4-D above 20 days year\(^{-1}\) was associated with a three-fold risk. Organophosphate, carbamate and chlorinated hydrocarbon insecticides were also associated with an increased risk. The study also examined the incidence of NHL in areas where ground water was contaminated with the pesticide Atrazine and nitrates from fertilizers. In areas of intense fertilizer use and where more than 20% of wells were contaminated by nitrate, NHL incidence increased two-fold [70]. These findings were confirmed in a study by Ward et al. [69]: long-term nitrate exposure from drinking water in rural areas was associated with an increased risk.

In another case–control study in Nebraska, Zahm et al. [297] investigated the risk of NHL in women who had been exposed to pesticides. The results showed that no risk was found for women who lived on farms, even if pesticides were used on the farm, but only a small number of women were recorded as actually mixing or spraying the pesticides. However, women who used organophosphate insecticides had a 4.5-fold increased risk of NHL. The risk from pesticides was augmented in women with a family history of cancer [297]. Farm workers exposed to carbamate pesticides, particularly Sevin, have been shown to have a 30–50% increased risk of NHL. In this study, farmers without carbamate pesticide use showed no increased risk of NHL [51].

Hardell & Eriksson [296] carried out a case–control study in Sweden to examine whether phenoxyacetic acids and other pesticides were important factors in the aetiology of NHL. The results showed that exposure to herbicides, particularly 4-chloro-2-methyl phenoxyacetic acid, and fungicides was associated with an increased risk. These findings concurred with a later study by Hardell et al. [291] in which associations were found for 4-chloro-2-methyl phenoxyacetic acid exposure and an increased risk of NHL and hairy cell leukaemia. Zahm et al. [297] demonstrated that rats acutely exposed to 2,4’-dichlorophenoxyacetic acid showed severe damage to their lymphoid organs.

Cantor et al. [290] obtained and cryopreserved serum samples from 25,802 participants in the Campaign Against Cancer and Stroke in Washington County, Maryland, USA in 1974. Subsequent analysis of the samples to determine levels of chlordane, lindane,
\(\beta\)-HCH, transnonachlor, heptachlor, heptachlor epoxide, oxychlordane, dieldrin, and HCB in the serum of NHL cases and matched controls found no association with increased NHL risk. However, there was a high coefficient of variation between sample sets in this study compared with their previous study, which may have introduced variance into the odds ratios, and consequently obscured a possible small association. The authors previously found evidence of an increased risk for PCBs but not DDT and related compounds [299].

Overall, there is a wealth of evidence implicating occupational exposure to pesticides and other organochlorines in NHL aetiology. However, is there evidence that background exposure to environmental contaminants may be involved in the aetiology of NHL?

A study by Hardell et al. [300] examined the effect of dioxins and dibenzofurans in a case–control study, which also calculated antibody titres for EBV. The results showed that the concentrations of dioxins and dibenzofurans were similar in cases and controls. However, for some higher chlorinated congeners, an increased risk was found in cases that had high titre to EA IgG (an antibody to EBV). The cases were then divided into two groups: low-grade NHL and high-grade NHL. For TCDD, an increased risk was found in the high-exposure and high-titre group for both categories of NHL. For low-grade NHL, the highest risks were found for cases with EA IgG > 80 and a high concentration of dioxins or furans, but no statistical significance was found. However, cases with high-grade NHL had a significantly increased risk with high antibody titre and high concentrations of 1,2,3,7,8-PeCDD (pentadioxin) and 2,3,4,7,8-PeCDF (pentafuran). For the majority of the higher chlorinated congeners of dioxins and dibenzofurans, an increased risk was found in the high-grade NHL group. The results of this study suggest that current exposure to particular organochlorines in combination with EBV may increase the risk for NHL. These results can be taken to represent background exposure because none of the cases or controls had been occupationally exposed to dioxins or furans.

The authors of the study also found a non-significant decreased risk in the low-titre and high-concentration group for some congeners of dioxins and dibenzofurans, which they state should be noted [300]. A similar previous study by Hardell et al. [292] found an increased risk for hairy cell leukaemia in patients with high antibody titres who were exposed to organic solvents, certain pesticides or impregnating agents compared with those subjects with low antibody levels who were not exposed.

Two studies discussed earlier in this section provide some evidence of background exposure to environmental contaminants and increased risk for NHL. The previously discussed studies in the USA that examined water that was environmentally contaminated with pesticides and nitrates showed an increased risk for NHL following long-term exposure [69,70].

A childhood case–control study carried out by the Children’s Cancer Group examined pesticide exposure in the home and risk for NHL. A significant risk for NHL was associated with the frequency of pesticide use in a domestic setting, with professional fumigations in the home, in utero and postnatal exposure. Increased risks were observed for T-cell and B-cell lymphomas, for lymphoblastic, large cell, and Burkitt morphologies. The increased risks were found both in young children, less than 6 years old, and in older children. Risks for specific pesticides were not examined in this study [293].

A recent article by Hardell & Eriksson [254] explored the hypothesis that the declining incidence in NHL seen in some developed countries may be a result of cancer prevention methods. The authors reviewed their own work and the work of others in which pesticides, persistent organic pollutants and other organochlorines were associated with an increased risk of NHL. In Sweden, between 1991 and 2000, NHL incidence declined by \(-0.8\) and
- 0.2%, respectively, for men and women. Phenoxyacetic acids and chlorophenols, which are pesticides, have been associated with NHL aetiology and these chemicals were banned in 1977. An increasing risk of NHL has also been linked with PCBs, HCB, chlordanes and dioxins. The highest exposure to these substances comes via the food chain, especially from meat and fish. An increased risk for NHL was suggested for high consumers of fish from the Baltic Sea, known to be contaminated by organochlorines [301]. Exposure to these persistent organic pollutants was highest in the 1960s and 1970s. However, there is evidence that the levels have declined, and consequently exposures should have decreased [287]. The levels of these pollutants have probably declined because of regulations put in place during the 1970s. The authors postulated that the change in incidence of NHL in Sweden and the other countries mentioned above could provide a good example of how regulation and precautionary measures to reduce exposure may be reflected in cancer incidence statistics in decades to come [254].

Discussion

There is little doubt that the cell signalling and intracellular control mechanisms required for the orderly co-existence of the different elements of a tissue are capable of being disrupted. Cancer, one of the possible outcomes of such a disruption, has undoubtedly affected multicellular organisms since they first evolved; there is evidence from dinosaur bones of cancerous lesions. The first written evidence of cancer as a disease afflicting Homo sapiens dates back to the time of the ancient Greeks and Egyptians. However, questions remain as to whether the incidence rate of cancer in these ancient civilizations was as high as in today’s industrialized societies, and the cause of any differences.

Almost 250 years have passed since the first association between cancer and environmental factors was noticed by Percival Pott. Today the widely cited figure is between 1 and 5% of all cancers being attributable to environmental factors [1]. Yet this conservative figure is called into question by twinning studies carried out by Lichtenstein et al. [26] and a mathematical study by Czene et al. [27], which showed that the environment rather than genetics predominates in the aetiology of cancer. Clearly, the environment plays a major role in cancer aetiology.

It has been estimated that up to two-thirds of cancers in developed countries are attributable to tobacco consumption and poor dietary habits [256,302]. It is possible that many of these cancers can be prevented through well thought out prevention measures and education programmes. However, the link between involuntary exposure to environmental contaminants and cancer is complex and it is extremely difficult to find any specific causal links because of this complexity. Thus, prevention measures have to rely on the precautionary principle, usually after the damage has been done.

The incidence of cancer worldwide is set to increase from 2000 levels by 50% by 2020 [3]. In addition, the majority of the increasing burden of cancer in both the developed and the developing world will be suffered by women [303]. Currently, the biggest burden of cancer is seen in affluent developed countries. However, as time passes, the prevalence of cancer is expected to rise in developing countries to similar levels to those found in developed countries [2]. This phenomenon can already be observed for breast cancer incidence [160]. A recent study by Wilson et al. [303], examining the changes in demography in developing nations and the subsequent effect on cancers in women, describes the irony that rising life expectancy in the developing nations, together with the embracing of ‘Western’ lifestyles, will result in many more people becoming vulnerable to cancer.
Although epidemiological studies do provide some evidence that pollutants may be involved in cancer aetiology, sceptics generally suggest that environmental contaminants, for example synthetic pesticides, which may show some endocrine-disrupting properties, are present at levels too low to cause harm. Thus, we have a vexed question: are humans exposed to environmental pollutants at sufficient levels to be a major factor in cancer aetiology? Some researchers suggest that environmentalists extrapolate results from adult animal tests performed at the maximum tolerable dose, to infer that low doses of the substance would be relevant to human cancer. It is also suggested that the amount of synthetic chemicals, such as pesticides, taken in via the diet pales into insignificance when compared with the amount of natural phytoestrogens taken in [77,122–126]. These two suggestions are flawed. In the first instance, many studies now show that environmentally relevant levels of substances do show responses such as endocrine-disrupting properties. These include low-dose effects following exposure to the environmental oestrogens bisphenol A and DES, where significant non-linear dose responses (U-shape) occurred at a dose lower than the no observed effect level observed by traditional animal testing models [119]. In the second instance, a biochemical mechanism by which relatively tiny amounts of synthetic pesticides may be carcinogenic compared with the relatively huge amounts of natural oestrogenic pesticides was suggested by Bradlow et al. [140].

Another reason given by sceptics is that many of the environmental substances that show oestrogenic properties are not potent oestrogens at low dose. Measuring oestrogenic potency is not sufficient to deem a substance incapable of endocrine disruption. For example, PCBs do not act directly at the oestrogen receptor, but exert their effects indirectly. For example, PCBs have been shown to suppress oestrogen sulphotransferase (SULTE1E1), which is responsible for the inactivation and excretion of oestradiol. Inhibition of this enzyme may increase local levels of oestrogen in oestrogen-sensitive tissues, for example the testis and mammary glands [101].

We should recognize that, despite improving 5-year mortality rates, every case of cancer that occurs is a personal tragedy for the patient and the immediate family. Surviving cancer, particularly childhood cancer, is not necessarily the final sequel. As many as two-thirds of childhood survivors will probably suffer a minimum of one late effect up to 5 years after diagnosis and possibly one quarter of late effects could be life-threatening [304]. Childhood survivors of cancer may face a diminished quality of life as a consequence of treatment toxicity [304–306]. Many parents and adult survivors of childhood cancer may not be fully aware of the possible consequences of their treatment. Table III shows a summary of the long-term side-effects of cancer treatment in childhood [305]. In a 20-year follow-up study,

### Table III. Long-term side-effects of childhood cancer therapy. Adapted from [302] (Grown copyright material is reproduced with the permission of the Controller of HMSO and the Queen's Printer for Scotland).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Predisposing factor</th>
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<tr>
<td>Growth retardation</td>
<td>Cranial irradiation</td>
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<tr>
<td>Delayed or precocious puberty</td>
<td>Cranial irradiation</td>
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<tr>
<td>Cognitive deficits</td>
<td>Cranial irradiation</td>
</tr>
<tr>
<td>Subfertility</td>
<td>Intrathecal methotrexate</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>High-dose cyclophosphamide</td>
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<td>Second malignancies</td>
<td>Gonadal irradiation</td>
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<td></td>
<td>Anthracycline use</td>
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<td></td>
<td>Epipodophyllotoxins</td>
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<td>Irradiation</td>
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<td>Alkylation agents</td>
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Humpl et al. [307] found a second malignancy rate of 3.25%, which was confirmed by a study by Neglia et al. [308]. In addition, adult survivors of childhood and adolescent cancer show higher death rates compared with their siblings, taking into account the primary cancer as a confounding factor [305]. In the developing world, it is thought that 100,000 children year\(^{-1}\) worldwide die needlessly and in pain because of a lack of affordable treatments [309].

As well as the obvious emotional and physical costs of cancer, there is a large economical cost. The cost of treatment and the loss of tax revenue to the economy while the patient undergoes treatment and during recovery is immense. In the UK in 1996, the direct cost of cancer treatment alone amounted to over £1 billion, accounting for about 6% of all National Health Service (NHS) expenditure. Government support for research into cancer is currently about £260 million [310]. The UK NHS Cancer Plan is being supported by the largest ever increase in funding for cancer services. In 2001, the NHS received an extra £280 million to improve cancer services, then a further £127 million in 2002, and by 2003/2004 the NHS was spending £570 million a year more on cancer services than it was in 2000/2001: an increase of 30% [311].

Cancer incidence also places a personal financial burden on families. A study in Australia and New Zealand by Dockerty and colleagues [312], which investigated the economic effects of childhood cancer on families, concluded that there is a large financial burden on families who have a child with cancer. Studies in the UK and USA came to the same conclusion. The mean total additional cost to families was around 13% of the family income. For eight of the families that took part in the study, the extra expenses amounted to 50% of the total family income [313,314].

There is mounting animal (experimental and wildlife) and human epidemiological evidence that environmental contaminants, particularly persistent organic chemical contaminants, are involved in the aetiology of cancer and that these chemicals exert their carcinogenicity at a time of development (prenatal, childhood, and adolescence). Thus, preventative measures to protect all people need to be put into place. An overall exposure reduction of bioaccumulative, persistent, carcinogenic and/or endocrine-disrupting chemicals should be planned. This should be based on the precautionary principle, thus accepting that there can be no reasonable prospect of identifying individual environmental pollutants as being the specific cause of particular tumours because of the complex mixture to which humans are exposed. Action will have to be taken in the absence of absolute scientific certainty.

In 1999, the Third European Ministerial Conference on Environment and Health, held in London, requested, in Paragraph 50 of the declaration, that the WHO should

promote and encourage public health measures into areas of emerging concern to children’s health on the basis of the precautionary principle.

It also states in the declaration

We recognize that exposure prevention is the most effective means of protecting children from environmental threats to health and we will develop prevention-oriented policies and actions [315].

In a poster by von Ehrenstein et al. [269] the authors point out that a good example of a precautionary approach related to children’s health protection is the European Union ban
on phthalates, which have been shown to have adverse health effects on the developing male reproductive tract and may be carcinogenic in humans. Phthalates were widely used as a plasticizer in PVC products. Many of these are products used specifically by children and infants, for example feeding bottles and plastic toys [316]. The ban is only in force until research provides conclusive data. It may make good health policy if this type of ban was used for all novel chemical substances and no exemptions were granted.

In a recent article, Hardell & Eriksson [254] noticed that NHL incidence declined in Sweden by −0.8 and −0.2%, respectively, for men and women during 1991–2000. They reasoned that the decline in NHL incidence may be a direct result of prevention measures put in place in Sweden in the 1970s. Phenoxycetic acids and chlorophenols, which are pesticides, have been associated with NHL aetiology and these chemicals were banned in 1977.

It is feasible that chemical environmental contaminants, in particular synthetic pesticides and organochlorines with endocrine-disrupting properties, could be major factors in cancer aetiology, particularly hormone-dependent malignancies such as breast, testicular and prostate cancers. The endocrine-disrupting properties of these compounds can perturb organogenesis and other developmental processes, such as mammary gland development. It would seem that there are critical windows during developmental processes when endocrine-disrupting chemicals can exert their effects and initiate cancers; for example, during female mammary gland development and male reproductive tract development. A chemical may have an adverse effect at one point in time but before or after that point in time the chemical may have no effects at all. Some similar reviews conclude that environmental exposures to carcinogenic or endocrine-disrupting chemicals exist at concentrations too low or have carcinogenic potential too weak to be considered a major factor in cancer aetiology. However, the evidence discussed in this review would dispute that claim; even if healthy adults are not at risk, it would seem that the developing foetus, infant, child and young adult are at risk. Studies discussed in this review show that low oestrogenic potency cannot be used as a marker of the capability of a chemical to cause oestrogenic responses and endocrine disruption.

As well as the timing of exposure, other variables need to be considered. Many people have genetic polymorphisms that may render them more susceptible to cancer initiation than a wild-type person following exposure to a substance with low oestrogenic potency. For example, the gene product p53 may have a modifying effect on organochlorine influence on breast cancer risk [195]. Women with at least one variant of the CYP1A1-exon 7 genotype have an increased risk of breast cancer associated with high serum levels of PCBs [193]. Unknown genetic susceptibility to cancer may account for a large proportion of the population. In addition, exposure to environmental pollutants may affect how aggressive the tumour is, possibly adversely affecting the prognosis.

Without doubt, governments and health organizations should be concerned about the increase in cancer incidence. Preventative measures other than education about tobacco, diet and the promotion of physical activity should be considered. Moreover, it seems to be the most vulnerable members of society, the developing foetus, the developing child and the adolescent, that are at risk of developing cancer following involuntary exposure to environmental contaminants. This may be an appropriate time for governments to adopt the precautionary principle, until all substances to which members of society are involuntarily exposed are proved safe from long-term, low-level effects on human and wildlife health, rather than treating the consequences. Moreover, the estimation that between 1 and 5% of malignant disease in developed countries is attributable to environmental factors may need revising upwards.
Acknowledgements

The authors gratefully acknowledge the assistance of Dr Annie Sasco, Dr C. Busby, Dr G. Staats-de Yanes, Ms V. Mountford, Ms Mary-Jo Hoare and Mr Steve Rowan. The help and support of the Cancer Prevention and Education Society is also gratefully acknowledged (www.cancerpreventionsociety.org).

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