EUROPEAN JOURNAL OF CANCER 44 (2008) 937–945

available at www.sciencedirect.com

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Review

# Systematic review of the association between circulating interleukin-6 (IL-6) and cancer

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ARTICLE INFO

*Article history:*
Received 14 February 2008
Received in revised form
29 February 2008
Accepted 29 February 2008
Available online 1 April 2008

*Keywords:*
Cancer
Epidemiology
Interleukin-6
IL-6
Systematic review

ABSTRACT

Our aim was to systematically review the epidemiologic evidence for an association of circulating interleukin-6 (IL-6), an inflammatory cytokine and cancer. We systematically searched electronic databases Embase, Medline and Web of Science for the studies of circulating IL-6 and any form of cancer. We identified and reviewed 189 discrete studies, consisting of 177 prevalent studies and three prospective studies. Cancer patients' IL-6 concentrations were higher than healthy controls' in most studies, but the results of investigations comparing IL-6 in cancer patients and individuals with benign diseases were less consistent. Due to the small number of prospective studies it is impossible to determine whether IL-6 is causally related to cancer. Large prospective studies of circulating IL-6 or studies using the functional variants of the IL-6 gene as instruments for circulating IL-6 concentrations would provide information on possible aetiological links between IL-6 and malignancy.



## 1. Introduction

Interleukin-6. (IL-6) is a pleiotropic inflammatory cytokine. First discovered as a B-cell growth factor, it is synthesised by many cell types, including T-cells, macrophages and stromal cells, in response to stimulation from tumour necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1).[1,2] The activation of the IL-6 complex activates Janus kinases (JAK), signal transducers and activators of transcription (STATs), which regulate cell proliferation and apoptosis.[3,4] In healthy adults, IL-6 concentrations over 10 pg/ml are considered abnormally elevated.[5] Blood IL-6 concentrations in humans follow a biphasic variation in any 24 h period, with peaks at about 19.00 and 05.00 h.[6]

High circulating IL-6 concentrations are associated with many diseases, including cardiovascular disease[7,8] and type 2 diabetes.[9] IL-6 may also have a role in cancer. IL-6 regulates chronic inflammation, which can create a cellular microenvironment beneficial to cancer growth.[10,11] It is also a growth factor for lymphatic, renal, bladder and colorectal cancer cells[12] and involved in the control of cell proliferation and apoptosis.[13] Despite the large number of publications the epidemiologic evidence for the role of IL-6 in cancer remains unclear and to our knowledge no one has previously systematically reviewed this literature. Therefore, in order to better understand the role of IL-6 in cancer and to suggest directions for future research, we conducted a systematic review to summarise the epidemiologic evidence for the association

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doi:10.1016/j.ejca.2008.02.047

between circulating IL-6 and any type of prevalent or incident cancer.

## 2. Materials and methods

Electronic databases Medline and Embase were searched systematically in December 2006. The Web of Science database was searched for publications citing the articles identified from previous searches, and papers cited in the reviewed articles were included where relevant. The search terms are detailed in Table 1. If the title or abstract of an article seemed relevant, the abstract or the complete article were reviewed. Two reviewers (K.H. and D.A.L.) independently extracted data from a sample of 30 publications using a standard data extraction sheet, and as the reviewers agreed on the extracted information over 95% of the time, one reviewer (K.H.) extracted the data from the remaining papers. Any uncertain issues were addressed by further joint inspection of the papers and discussion (with DAL).

The main inclusion criterion for the studies was that they must include results of circulating IL-6 concentrations in individuals with and without cancer. Studies of any type of cancer in humans, written in any language were included. Where more than one paper had been published using data from the same participants, all publications were reviewed, but only the latest, largest or the most completely reported article was included in the summary of studies.

The main exclusion criterion for the studies was that they did not contain the results of IL-6 concentrations in cancer patients as well as cancer-free people. We also excluded studies of IL-6 in cell-lines, tissue samples or bodily fluids other than blood and studies in which only IL-6 gene polymorphisms were measured. We did not review the studies of the serum soluble IL-6 receptor because there is evidence that its relationship with circulating IL-6 is ambiguous.[14,15]

**Table 1 – Search terms**

| MeSH terms | Text words |
|---|---|
| Neoplasms **OR** Neoplasms, second primary | cancer$ **OR**malign$ **OR** tumour$ **OR** tumor$ |
| AND | |
| Interleukin-6 | Interleukin-6 **OR** interleukin-6 **OR** interleukin-6 **OR** IL-6 **OR** IL6 **OR** IL 6 |
| AND | |
| Epidemiologic studies/ | • Case–control$ **OR**<br>• (cohort adj1 (study or studies)) **OR**<br>• cohort analy$ **OR**<br>• (follow up adj1 (study or studies)) **OR**<br>• (observational adj1 (study or studies)) **OR**<br>• longitudinal.tw. retrospective.**OR**<br>• cross-sectional.tw. associat$ **OR**<br>• comparative study/ |

## 3. Results

### 3.1. Studies

Our Medline search found 2026 and the Embase search found 2487 potentially relevant publications. These abstracts were reviewed and 279 potentially relevant studies identified (Fig. 1). Eighty-one studies did not fulfil the inclusion criteria and were excluded; 198 studies contained relevant data and were reviewed. The main characteristics and findings of the studies of circulating IL-6 and cancer identified in our systematic review are described in detail in Web Tables W1-W21. There were nine duplicate publications among the papers on multiple myeloma, breast, lung, colorectal, head and neck and soft-tissue cancers.[16–24] We reviewed the duplicate publications but excluded them from our summary of the results. One study which included previously published data but added a number of new participants was included in the results summary as a discrete study.[25] We post hoc excluded two studies on multiple myeloma[26] and oesophageal cancer[27], in which IL-6 seemed to have been measured in cancer patients and cancer-free controls but only the cancer patients' IL-6 data were published and our attempts to obtain the controls' data from the authors failed. Despite our efforts, we were unable to have two Japanese articles on paraproteinemias and colorectal cancer translated[28,29], but we included the data that we were able to extract from the abstracts and tables only. Other non-English publications were successfully translated in full.

After all exclusions, we were left with 189 discrete studies. The cancer types examined in the studies included in our review are summarised in Table 2. The most commonly studied cancers were multiple myeloma, lymphatic, lung, colorectal and ovarian cancers. Investigating the association between IL-6 and cancer was the main aim in 100 discrete studies, but we also identified 89 studies with other primary aims, which also presented results of IL-6 concentrations in cancer patients and cancer-free people. Due to the different comparison groups and cancer outcomes we decided it would be inappropriate to pool the results of the studies in a meta-analysis.

Summarising the results of 189 discrete studies does not do justice to the wealth of information these studies contain. Therefore, here we describe the overall design features and findings of the studies of circulating IL-6 and cancer, in order to provide an overview of the state of the art in this area of research to inform current and future investigators. In addition, details of the main characteristics and findings of the studies of circulating IL-6 and cancer are given in Web Tables W1-W21 and a detailed description of the study results, by cancer type, is provided in the Web Supplement, together with a complete list of references.

#### 3.1.1. Study design and selection of controls

There were 177 prevalent case–control studies and nine cross-sectional studies. We identified only three prospective studies; two case–control studies nested in prospective cohorts[30,31] and one prospective cohort study.[32]

Overall, few studies provided an adequate description of the selection of the cancer-free comparison group. Most studies identified in our review included multiple control groups, e.g. both healthy controls and controls with non-malignant

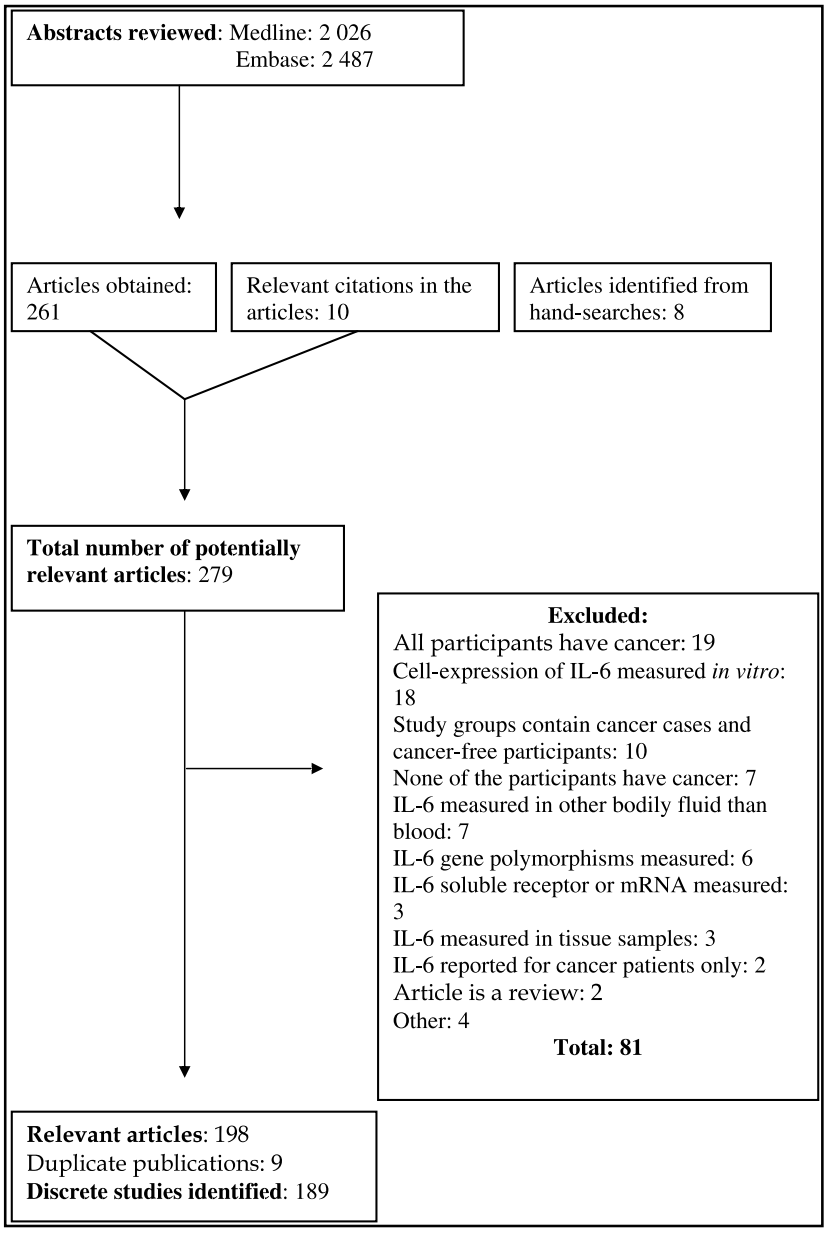


**Fig. 1 – IL-6 systematic search results.**

diseases. Community controls (representative of the population from which the cases come) were recruited in 13 prevalent case–control studies, one cross-sectional study, two prospective nested case–control studies and one prospective cohort.[33–49] Whilst the selection of controls may have introduced bias to some studies, the inclusion of both healthy controls and controls with benign diseases is an advantage as comparing IL-6 concentrations in cancer patients and controls with other diseases provides some evidence of whether elevated IL-6 is specific to malignancy or non-specifically associated with any disease process.

### 3.2. *Adjustment for potential confounders*

It would be unreasonable to expect the studies in which examining the association between IL-6 and cancer was not the main aim to control for confounding in their analyses, but lack of adjustment is a limitation in studies in which this association is the focus of the research. We would consider that at least age, sex and tobacco smoking ought to be controlled for in the studies of circulating IL-6 and cancer. Additional adjustment should be made for socioeconomic position, body fatness and other factors that could confound the association of IL-6 with some cancer types, for example, adiposity strongly associated with IL-6[50,51] as well as many cancers.[52] Overall, in few of the studies with IL-6 in cancer as the main aim had the investigators adequately controlled for possible confounding. Twenty-two studies had adjustment for potential confounders, most commonly age, sex, smoking or body mass index (BMI) (Tables W1-W21). Other factors causing elevated IL-6 concentrations are infection, which might also effect cancer outcomes, and surgery. In many studies, the investigators

**Table 2 – Studies of circulating IL-6 and cancer, by cancer type**

| Cancer type | Number of discrete studies containing relevant results | Number of discrete studies with prevalent design[a] | Number of discrete studies with prospective design[a] |
|---|---|---|---|
| Multiple myeloma | 22 | 22 (4) | – |
| Lymphatic | 21 | 21 (5) | – |
| Lung | 18 | 17 (0) | 1 (1) |
| Colorectal | 17 | 16 (0) | 1 (1) |
| Ovarian | 16 | 16 (0) | – |
| Leukaemia | 12 | 12 (4) | – |
| Pancreatic | 11 | 11 (0) | – |
| Prostate | 11 | 9 (0) | 2 (1) |
| Gastric | 10 | 10 (0) | – |
| Liver | 9 | 9 (0) | – |
| Head and neck squamous cell carcinoma | 8 | 8 (0) | – |
| Breast | 8 | 7 (0) | 1 (1) |
| Renal cell carcinoma | 7 | 7 (0) | – |
| Melanoma | 6 | 6 (0) | – |
| Soft-tissue sarcomas | 4 | 4 (0) | – |
| Uterine | 3 | 3 (0) | – |
| Bladder | 2 | 2 (0) | – |
| Cervical | 1 | 1 (0) | – |
| Bone sarcoma | 1 | 1 (0) | – |
| Multiple cancer types | 22 | 19 (8) | 1 (1) |

a Numbers in brackets indicate the number of studies also containing other cancers, which were analysed as separate sub-groups.

had excluded potential participants with infections. In order to minimise the effect of any invasive procedure, the researchers in most of the studies reviewed here had sampled sera from the participants before the onset, or at least four weeks after surgery or other therapies.

### 3.3. *IL-6 in diagnosis of cancer*

In 29 studies, the researchers stated that their aim was to investigate circulating IL-6 concentrations in cancer diagnosis, but most of them did not report appropriate tests of diagnostic accuracy (Web Tables W1-W21). In one case–control study IL-6 had 67.6% sensitivity and 58.3% specificity in discriminating pancreatic cancer from pancreatitis at a cut-off value of 5 pg/ml.[53] In a second case–control study, with a higher cut-off value of 49.2 pg/ml, IL-6 had 66% sensitivity and 95% specificity in discriminating bladder cancer from cystitis[54], and in a third that IL-6 had 71.1% and 90% sensitivity and specificity in discriminating between cholangiocarcinoma and benign biliary disease with a cut-off of 0.18 ng/ml.[55] IL-6 was reported to have 77% sensitivity and specificity in differentiating between malignant and benign ovarian tumours.[56] However, it is difficult to draw conclusions of the diagnostic use of circulating IL-6 in cancer based on this limited number of studies of different cancer types.

### 3.4. *IL-6 in aetiology of cancer*

Only three studies had a prospective design and could thus provide robust evidence of a possible aetiological link between IL-6 and cancer. The design, participant selection and the main findings of the prospective studies are summarised in Table 3. In the Health ABC cohort (including 2438 elderly participants and 296 incident cancer cases) the investigators reported a multivariable-adjusted HR for any cancer of 1.13 (95% CI: 0.94, 1.37) per natural log unit increase in IL-6; the HRs for subgroups of colorectal and lung cancers were similar, but no association was found with prostate and breast cancers.[57] In a case–control study nested in the Multicenter AIDS Cohort Study (MACS) higher mean IL-6 concentrations were found in HIV-infected men who went on to develop lymphoma (mean IL-6. pg/ml: 42, SD: 18) than in those who had AIDS but did not develop cancer (mean IL-6, pg/ml: 9.8, SD: 6.5) or were HIV-positive (mean IL-6, pg/ml: $\leqslant$1.0, $p = 0.001$).[58] In another case–control study, nested in the San Antonio Center for Biomarkers of Risk of Prostate Cancer cohort, the investigators reported a multivariable-adjusted odds ratio of 0.93 (95% CI: 0.42, 2.06) (highest vs. lowest tertile of IL-6) for incident prostate cancer.[59]

## 4. Discussion

The role of inflammation in cancer in general and certain forms of cancer in particular has been the focus of extensive research.[60] Determining whether an association between inflammatory markers, such as IL-6, and cancer exists, and understanding the nature (causal or otherwise) of any association are important because such knowledge could inform preventative strategies or help in the development of methods for early diagnosis of cancer.

IL-6, first identified as a B-cell growth factor, is an important regulator of immune cell growth and differentiation, and therefore the most commonly studied cancer types in relation to circulating IL-6 concentrations are immune cell cancers, particularly multiple myeloma and lymphatic cancers. Experimental studies have shown that IL-6 is a growth factor for multiple myeloma, renal cell carcinoma, non-Hodgkin's lymphoma, bladder cancer and colorectal cancer cells[61] and acts together with other cytokines in producing other

**Table 3 – Summary of prospective studies of circulating IL-6 and cancer**

| Study, (author, year) | Design | N participants | Age of participants | N (%) female | Main aim | Main findings | Comments |
|---|---|---|---|---|---|---|---|
| Multi-centre AIDS cohort study (MACS), US (Breen et al., 1999) | Prospective case–control nested in a cohort | Lymphoma: 50<br>AIDS: 44<br>HIV+: 48<br>HIV–: 44 | Not cited | 0 (0) | Aetiology to examine whether serum IL-6 and soluble CD23 predict lymphoma of the Burkitt's/ small non-cleaved cell subtype | Mean (SE) IL-6, pg/ml:<br><br>Lymphoma: 42 (18)<br>AIDS: 9.8 (6.5)<br>HIV+: $\leqslant$1.0<br>HIV–: 3.9 (1.7)<br>$p > 0.05$<br>Median IL-6, pg/ml, by lymphoma type:<br><br>Burkitt's/small non-cleaved cell: 12<br>Large cell: $\leqslant$1<br>Immunoblastic: $\leqslant$1<br>Central nervous system: $\leqslant$1<br>$p = 0.01$ | Controls selected from participants in the same cohort as cases, and three controls, one with AIDS, one HIV+ and one HIV– were matched to each case by visit number and, where possible, by CD4+ T cell count<br>Cancer patients' IL-6 measured before any surgery and not during any chemo- or radiotherapy<br>Results may have been influenced by the large number of participants with undetectable IL-6 ($\leqslant$1 pg/ml) concentrations in all participant groups |
| Health ABC study, Memphis, TN and Pittsburgh, PA, US (Il'yasova et al., 2005) | Cohort | Cancer-free participants: 2169<br>Incident cancers: 296<br><br>Colorectal cancer (CRC): 40<br>Lung cancer: 42<br>Breast cancer: 30<br>Prostate cancer: 63 | Median (IQR):<br><br>Cases: 74 (71–76)<br>Non-cases: 73 (71–76) | Cases: 113 (38)<br>Non-cases: 1193 (55) | Aetiology to analyse the association between circulating inflammatory markers and incident cancer in elderly people | HR [95% CI] for incident cancer events/ log IL-6, pg/ml:<br><br>Crude: 1.18 [0.98–1.41]<br>Adjusted: 1.13 [0.94–1.37]<br>Adjusted and NSAID users excluded: 1.10 [0.90–1.35]<br>Multivariable-adjusted HR [95% CI] for cancer events by type/log IL-6, pg/ml:<br><br>CRC: 1.44 [0.90–2.31]<br>Lung: 1.43 [0.91–2.26]<br>Prostate: 0.88 [0.59, 1.30]<br>Breast: 0.95 [0.54, 1.65]<br>Additional adjustment for smoking:<br>Lung: 1.22 [0.75, 1.97] | Participants recruited from Medicare beneficiaries; exclusion criteria were difficulty in walking mile, climbing 10 steps or doing the basic daily activities, life threatening illness or intent to leave area in the subsequent 3 years<br>Adjustment for age, gender, race and site; further adjustment for BMI, pack-years of cigarettes smoked, physical activity, education, baseline medical conditions and medication used did not change the effect estimates (data not shown)<br>Cancer patients' IL-6 measured before any surgery and not during any chemo- or radiotherapy<br>Any incident cancer group also included gastrointestinal cancer cases |

(*continued on next page*)

**Table 3** – *continued*

| Study, (author, year) | Design | N participants | Age of participants | N (%) female | Main aim | Main findings | Comments |
|---|---|---|---|---|---|---|---|
| San Antonio Center for Biomarkers of Risk or Prostate Cancer cohort, San Antonio, TX, US (Baillargeon et al., 2006) | Case-control nested in a prospective cohort | Prostate cancer: 125<br>Healthy controls: 125 | Mean (SD):<br><br>PC: 63.5 (7.4)<br>Controls: 63.2 (7.6) | 0 (0) | Aetiology and prognosis to examine the relationship between obesity and leptin, adiponectin and interleukin-6 with prostate cancer risk and aggressiveness | Age-adjusted OR [95% CI] by tertiles of IL-6, pg/ml:<br><br>Incident prostate cancer:<br>1st: 1.00 (ref.)<br>2nd: 1.09 [0.61, 1.93]<br>3rd: 0.84 [0.46, 1.53], $p = 0.98$<br><br>High-grade prostate cancer (Gleason score>7):<br>1st: 1.00 (ref)<br>2nd: 1.82 [0.75, 4.44]<br>3rd: 0.84 [0.30, 2.33], $p = 0.17$<br>Multivariable-adjusted OR [95% CI] by tertiles of IL-6, pg/ml:<br><br>Incident prostate cancer:<br>1st: 1.00 (ref.)<br>2nd: 1.63 [0.75, 3.65]<br>3rd:0. 93 [0.42, 2.06], $p = 0.63$<br><br>High-grade prostate cancer (Gleason score>7):<br>1st: 1.00 (ref)<br>2nd: 1.35 [0.52, 3.52]<br>3rd: 0.85 [0.29, 2.47], $p = 0.52$ | Cases and controls selected from the participants of a community-based prostate cancer screening cohort; all men were free prostate cancer at study baseline<br>Cancer-free participants were age-matched to cancer cases<br>Cancer patients' IL-6 measured before any surgery and not during any chemo- or radiotherapy<br>Multivariable-adjusted models adjusted for age, race, serum PSA, BMI, leptin and adiponectin |

tumour-promoting signals.[62,63] Built upon the knowledge of the biological functions of IL-6, the epidemiologic research into the role of circulating IL-6 in malignancy has focused on immune cell cancers, and the results from these studies suggest that elevated IL-6 is associated with multiple myeloma and lymphomas.

Overall, in the studies we reviewed cancer patients' IL-6 concentrations were elevated when compared to healthy controls in most studies of prevalent cancer cases, but among the studies comparing cancer patients to individuals with non-malignant conditions, the evidence for an association was less clear. Few studies published thus far included results from adequate diagnostic tests for the use of circulating IL-6 on cancer diagnosis. Furthermore, prevalence studies can neither establish nor exclude a causal association, although these are useful in generating hypotheses on causality. As only three of the 189 discrete studies had a prospective design, it is impossible to assess the role of IL-6 in cancer aetiology from the currently available evidence. The results from two prospective studies suggest that IL-6 is associated with an increased risk of colorectal or lung cancers and cancer in general, but no association with prostate cancer risk was observed. However, the effect estimates in these studies were imprecise due to the small number of cancer cases. In the third prospective study elevated IL-6 concentrations were associated with lymphoma in HIV infected homosexual men, but the generalisability of these results to other populations is uncertain.

In addition to prospective studies, gene-association studies using the principles of Mendelian randomisation would provide insights into the role of this cytokine in cancer aetiology.[64] As gene variants are randomly allocated at conception, any associations of genetic polymorphisms and cancer outcomes are not confounded by socioeconomic or lifestyle factors nor affected by reverse causality.[65] Investigating associations of IL-6 genetic variants with cancer would thus provide a way to overcome these potential biases.[66] The results from three population-based case–control studies suggest that IL-6 gene polymorphisms are related to the risk of colorectal cancer[67], non-Hodgkin's lymphoma[68] and plasma cell cancers.[69] IL-6 gene variants have also been found to be associated with an increased risk of oral[70] and cervical[71] cancers, but the findings of two studies of gastric cancer are contradicting.[72,73] A recent systematic review of studies examining IL-6 gene and breast cancer risk suggest that IL-6 gene polymorphisms do not have a significant role in breast cancer.[74] As it is important to replicate the findings of genetic association studies in different populations, further studies are needed to confirm these findings.

Our review demonstrates a massive research effort in examining the role of IL-6 in malignancy. The most important conclusion of this review is that circulating IL-6 is associated with some cancers but, despite the abundance of published studies, we still do not know whether circulating IL-6 is useful in the diagnosis of cancer or relevant to its aetiology. Therefore, instead of further studies of prevalent cancer cases, future research resources would be best used for large prospective studies or gene-association studies to investigate the role of IL-6 in the diagnosis and aetiology of cancer.

## Conflict of interest statement

None declared.

## Acknowledgements

D.A.L is funded by a (UK) Department of Health career scientist award and when this work was conducted, K.H. was funded by the (UK) Medical Research Council PhD Studentship. We thank Guobing Lu and Leona Gabrysova for their assistance in translating foreign language papers for this review.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2008.02.047.

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