# Cancer diagnostics: current concepts and future perspectives

The World Health Organization (WHO) (1) has recently released reliable data about the global epidemiology of cancer. Overall, cancer is one of the most common diseases, with as many as 14 million new cases each year and accounting for over 8.8 million deaths around the globe. These notable figures are further aggravated by future projection of incidence and prevalence, wherein the total number of new cancer cases is predicted to increase by over 70% over the next 2 decades, paralleled by a similarly increasing number of deaths (*Figure 1*). Notably, the total expenditure for cancer totaled approximates 125 billion US$ in 2010 in the United States, and is projected to increase to over 150 billion US$ in 2020. Lung cancer is the most frequent cause of death for cancer worldwide (1.69 million deaths), followed by hepatic malignancies (788,000 deaths), colorectal (774,000 deaths), gastric (754,000 deaths) and breast (571,000 deaths) cancers (2).

Like many other human chronic conditions, cancer is a clearly preventable disease. Notably, the World Cancer Research Fund has recently estimated that over 32% of cancer deaths can be avoided by ceasing cigarette smoke, whereas approximately 20% of all cancers may be prevented by reducing overweight, enhancing physical activity, limiting alcohol consumption, improving the nutritional status (2), but also reducing environmental or occupation exposure to carcinogenic substances. Irrespective of the unquestionable role of prevention in limiting the dramatic epidemiological burden of cancer, screening and early diagnosis are the cornerstones for establishing a timely therapeutic management, which may contribute to save many lives worldwide.

Unlike many other life-threatening diseases such as acute coronary syndrome (3) and diabetes (4), laboratory diagnostics of cancer has been for long hamstrung. Despite many efforts have been made in the past decades, the armamentarium of *in vitro* diagnostics has remained considerably narrow in cancer, and mostly limited to the early diagnosis of specific malignancies, such as prostate cancer by means of prostate specific antigen (PSA) testing (5), or colorectal cancer with fecal occult blood (FOC) screening (6). Neither the use of traditional cancer biomarkers alone, nor their integration within cancer detection models by means of machine learning (7), were found to be clinically useful for screening occult cancers in the general population. Therefore, this approach must be firmly discouraged and additional strategies should be implemented. This special issue of Annals of Translational Medicine has hence been planned to provide an overview of current concepts and future perspectives in cancer diagnostics.

In the first article of this issue, Comelli *et al.* present the result of a large retrospective study aimed to define the epidemiology and clinical presentation of brain cancers firstly diagnosed in a large urban emergency department (ED) (8). Although the overall prevalence of first ED diagnoses of these tumors was found to be globally low compared to all ED visits (205/870,135; ~0.02%), the over 200 cases recorded throughout the 10-year study period should be regarded as meaningful numbers, so emphasizing the concept that all the emergency physicians should clearly acknowledge this possibility.

In the second article of this issue, Mantovani and Targher (9) provide a consistent overview about the relationship between type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma. More specifically, the authors discuss the epidemiological evidence linking these conditions and the putative biological pathways, which may be actually involved for supporting the increased risk of hepatocellular carcinoma in diabetics. In a further article of this issue Goyal and Hu analyze the intriguing relationship between anisocytosis and hepatocellular carcinoma (10). Briefly, the authors conclude that the red blood cell distribution width (RWD), a reliable measure of erythrocyte volume heterogeneity, should now be considered a clinically efficient marker of disease severity and fibrosis in patients with liver cirrhosis as well as in those with NAFLD, also providing important clues about the possible interplay between RDW and hepatocellular carcinoma.

In another article of this issue, Danese *et al.* aim to investigate a highly debated issue in cancer epidemiology, which is the relationship between mobile phone radiofrequency exposure and future risk of cancer (11). Although the International Agency for Research on Cancer currently classifies radiofrequency exposure as a possible carcinogenic in humans, the results of this experimental study convincingly show that DNA integrity of human lymphocytes exposed to a conventional 900 MHz radiofrequency emitted by a conventional smartphone for up to 30 min is not significantly impaired, thus raising additional doubts as to whether a moderate use of mobile phones may be really considered a risk factor for malignant transformation.

Myelofibrosis, either arising as a de novo condition or evolving from a previous polycythemia vera or essential

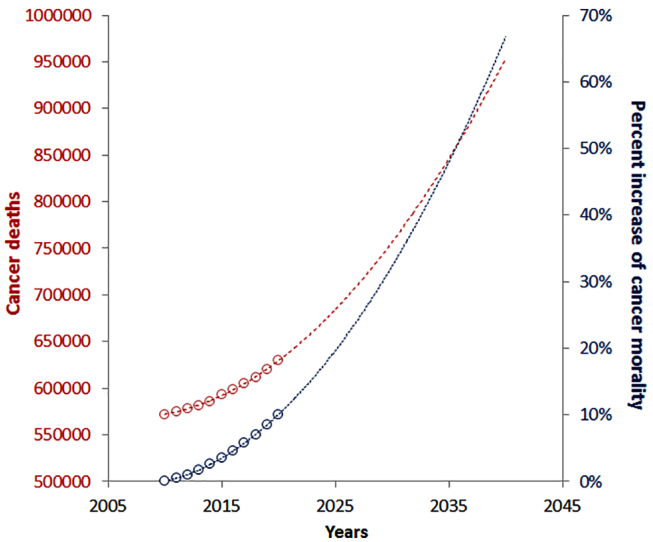


**Figure 1** Projections of cancer deaths in the United States, years 2010–2040.

thrombocythemia, is a chronic myeloproliferative disease characterized by a clonal expansion of hematopoietic progenitors. PKC epsilon has been earlier recognized as cancerogenic protein, which promotes cancer survival and invasiveness, but also playing a pivotal role in aberrant megakaryocytopoiesis in myelofibrosis (12). In an additional article of this special issue of *Annals of Translational Medicine*, Masselli *et al.* demonstrate that PKC epsilon is significantly over-expressed in myelofibrosis patients compared to healthy subjects (13). Moreover, the platelet expression of PKC epsilon was also found to be associated with high-risk disease and positive history of major cardiovascular events in patients with myelofibrosis, so highlighting the potential clinical usefulness of this protein as an index of disease aggressiveness and thrombotic risk in myelofibrosis.

A number of contributions specifically aimed to investigate the role of traditional and innovative cancer biomarkers then follow these valuable epidemiological papers.

In the first of these articles, Gion *et al.* discusses the important issue of appropriateness of tumor marker ordering (14), one of the most relevant and actual issues in laboratory medicine (15). Briefly, the article describes the importance of implementing evidence-based information and monitoring their impact on clinical practice as an essential aspect for improving appropriateness, reducing costs and safeguarding patient safety in health care.

In a following article, Montagnana *et al.* explore the rather controversial issue of circulating biomarkers in diagnosing epithelial ovarian cancer (16). With the awareness that serum biomarkers such as CA125 and human epididymis protein 4 (HE4) are not enough sensitive or specific for early diagnosis of ovarian cancer, the authors discuss the attractive perspectives emerging from the use of other circulating molecular biomarkers such as micro RNAs (miRs).

In a similar article, Santangelo *et al.* provide a comprehensive insight into the *in vitro* diagnostics of gliomas (17), a type of tumors for which the current armamentarium of circulating biomarkers is virtually valueless. As for ovarian cancer, the measurement of miRs is regarded as an intriguing perspective, despite the many current drawbacks that still plague the assessment of these biomarkers, which are thoughtfully discussed in this article.

In the next article of this issue, Köhn *et al.* aim to discuss the role of liquid biopsy in lung cancer diagnostics (18). The authors highlight that this strategy may be seen as a valuable perspective for monitoring treatment response, for early identifying resistance to targeted therapy, thus offering a valuable resource for personalizing the therapeutic approach according to the genetic fingerprint of the tumor.

Danese and Montagnana (19) then provide additional insights about the role of epigenetics in cancer diagnostics. In their comprehensive overview about the epigenetics of colorectal cancer, the authors discuss the major advancements in genomic technologies that have promoted the identification of a number of epigenetic alterations involved in cancer initiation and

 

progression such as DNA hypomethylation, promoter hypermethylation and miRs dysregulation.

In the last article of this issue, Melichar *et al.* discuss the role of measuring neopterin in cancer diagnostics (20). Specifically, the authors point out that increased urinary or serum neopterin concentrations predict poor prognosis in cancer patients. Therefore, it can be concluded that neopterin measurement may be a valuable perspective for cancer monitoring.

In conclusion of the preface of this special issue of *Annals of Translational Medicine* on cancer diagnostics, we wish to thank all the authors to for their valuable contribution, hoping that these articles may be of interest for the readership of the journal.

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