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Review

Endotoxin and cancer chemo-prevention

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ABSTRACT

Reduced rates of lung cancer have been observed in several occupational groups exposed to high levels of organic dusts contaminated by endotoxin. The underlying anti-neoplastic mechanism of endotoxin may be an increased secretion of endogenous anti-neoplastic mediators and activation of the toll-like receptors (TLR). A detoxified endotoxin derivative, Monophosphoryl Lipid A (MPL®) is marketed in Europe since 1999 as part of the adjuvant systems in allergy vaccines for treatment of allergic rhino-conjunctivitis and allergic asthma. Over 200,000 patients have used them to date (nearly 70% in Germany). Since detailed exposure (MPL® dose and timing of administration) and individual data are potentially available, an observational follow-up study could be conducted in Germany to investigate the protective effect of MPL® against cancer, comparing cancer incidence in two groups of patients with allergic rhinitis: those treated with allergoids plus MPL® and those treated with a vaccine including the same allergoids but not MPL®. The protective effect of MPL® could be quantified in ever and never smokers. If this proposed observational study provides evidence of protective effects, MPL® could be immediately used as a chemo-preventive agent since it is already in use as adjuvant in human vaccines against cancer.

1. Background

1.1. Cancer mortality and incidence

The US age-standardized mortality rate per 100,000 for heart disease and cancer were, respectively, 492.7 vs.198.6 in 1970, and 173.7 vs. 168.6 in 2011 [1]. A scatter-plot of rates against years was built from 1993 to 2011 with a slope expressing the time trend. Fig. 1 shows that the time trends for cancer and heart disease are expected to converge after 2011, when cancer will likely become the leading cause of death. The crossover of cancer over heart disease mortality has been recently reported in New Zealand [2], France [3–5], Spain [3], Canada [6] and the Netherlands [7].

High-quality population-based cancer incidence data have been collected throughout the world since the early 1960s and published periodically in Cancer Incidence in Five Continents (CI5). The International Agency for Research on Cancer (IARC) has made these data available [8]. These data have been used in Fig. 2a (males) and b (females), to show the time trend of age-standardized (world) cancer incidence rates (all ages) from the first available to the last available calendar year in 12 Western countries. A general upward trend over time appears in both figures.

Cancer is a major public health issue worldwide in both developed countries (where incidence rates are higher) and developing countries (where survival rates are lower). However, cancer incidence is increasing also in developing countries as a consequence of the globalization of economies/habits and the high frequency of cancers of infectious origin. The majority of patients diagnosed with cancer are likely to die for the disease sooner or later, and nevertheless their survival is inevitably going to impact the corresponding treatment costs. In the next future the cost will raise even more sharply because of the introduction of new targeted cancer treatments [9], particularly in countries such the US where a twofold increase of the elderly population is expected in the next decades [10].

1.2. Current preventive strategies against cancer

Although previous observational studies showed that cancer could be prevented by a high intake of fruits and vegetables, the European Prospective Investigation into Cancer and Nutrition cohort (142,605 men and 335,873 women) provided evidence of a very small inverse association between fruit and vegetable intake and cancer risk [9]. Likewise, in two prospective cohorts (71,910 women in the Nurses' Health study and 37,725 men in the Health Professionals' Follow-up Study) healthy eating based on a fruit and

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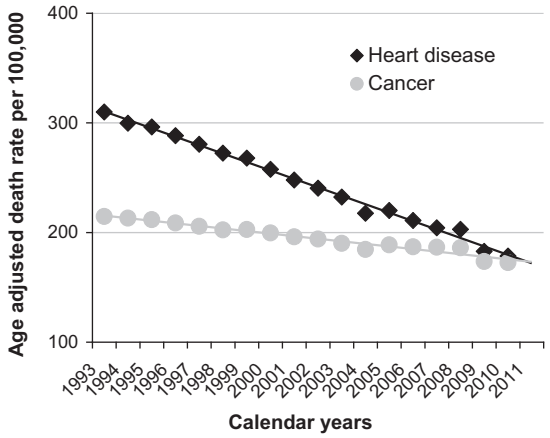

Fig. 1. Age adjusted (US standard population 2000) death rates per 100,000 for heart disease and malignant neoplasms. USA, both sexes, all ages and races, 1993–2010.

vegetable diet proved to be effective in reducing cardiovascular diseases but not cancer incidence [11,12].

Despite numerous advances in tobacco-dependence treatment, the U.S. adult smoking prevalence and quit rates have stalled [13–15]. According to Levy et al. [16] the annual smoking cessation without any intervention is estimated to be 4.3%, reaching a rate of 4.5–10% with corporate health education campaigns requiring great effort and resources. Furthermore relapse rates after cessation are reported to be as high as cessation according to Hughes et al. [17], Hajek et al. [18] and Anderson et al. [19]. Yet efforts to prevent teens from taking up smoking have shown no evidence of long term effectiveness [18,20], and ex-smokers continue to have an elevated risk of developing lung cancer [21].

Prevalence of binge and heavy drinking among adults in the United States has been practically constant from 1993 to 2009, with approximately 5% of the total population drinking heavily and 15% binge drinking [22]. This signifies that health education campaigns have failed to achieve significant public health outcomes in alcohol misuse reduction. According to Foxcroft et al. [23] no firm conclusions can be drawn on the effectiveness of short and medium term primary interventions to combat alcohol misuse in young people.

Despite the afore mentioned evidence, the International Union Against Cancer (UICC) still suggested in 2005 the same key areas for cancer prevention: smoking, alcohol misuse, obesity, sun exposure, and infections [24].

All the above calls for a revision of prevention strategies against cancer: a reduced incidence would indeed almost certainly translate directly into reduced mortality.

2. Discussion

2.1. Endotoxin and cancer

Endotoxin is an integral component of the outer wall of Gram-negative bacteria which grow on moist cellulose-rich materials (organic dusts). The more active component of endotoxin, lipopolysaccharide (LPS), is liberated when the bacteria die and the cell wall breaks apart [25,26]. Endotoxin is ubiquitous in indoor and outdoor environments, but the highest exposures have been measured in agricultural environments and cotton textile mills [27]. Exposure primarily occurs through inhalation of airborne endotoxins present in organic dusts (also termed bioaerosols).

Endotoxin exposure may cause acute and chronic health effects. However, epidemiological studies have also shown protective effects of environmental endotoxin exposure with regard to atopic asthma and allergy in early childhood [28]. Another positive effect of endotoxin is suggested in the context of cancer: reduced rates of lung cancer have been observed in several occupational groups which are exposed to high levels of organic dusts contaminated by endotoxin.

A systematic review and meta-analysis was conducted on the large body of epidemiological data published on farmers and cotton textile workers [29]. The summary risk of lung cancer was 0.72 (95% Confidence Interval, CI = 0.57–0.90) in the latter (Fig. 3a) and 0.62 (95% CI: 0.52–0.75) (Fig. 3b) in the former.

In Italy exposure to endotoxin has never been measured in dairy stables. The number of dairy cattle in the farm was therefore used as a surrogate of exposure levels to endotoxin. An inverse relationship was observed between standardized mortality ratio or adjusted odds ratio for lung cancer and the number of dairy cattle in the farm [30,31]. The protective effect was no more discernible among farmers who had ceased working in dairy farms >15 years previously [31]. Concordant results were obtained for Finnish farmers [32].

One study from China [33] and another from Lithuania [34] provided quantitative estimates of endotoxin exposure and both studies tended to support a dose–dependent protective effect of endotoxin on lung cancer risk. In the large study on Chinese workers, cumulative exposure to endotoxin was inversely related to risks of lung cancer (p-trend = 0.004) [33] and also: esophageal cancer (p-trend = 0.01) [35]; stomach cancer (p-trend = 0.001) [35]; rectum cancer (p-trend = 0.08) [36]; liver cancer (p-trend = 0.02) [37]; pancreatic cancer (p-trend = 0.001) [38]; and breast cancer (p-trend = 0.001) [39].

The underlying anti-neoplastic mechanism of endotoxin may be an increased secretion of endogenous anti-neoplastic mediators (cytokines and tumor necrosis factor-alpha), and activation of the toll-like receptors (TLR) [40] (see Fig. 4). TLRs are intracellular and cell surface proteins of the innate immune system that are capable of recognizing pathogen-specific molecules; TLRs are expressed by several immune cells including dendritic cells (DC) where they act as a master regulatory switch and play an important role in reversing the immune tolerant effects of T cells.

2.2. Monophosphoryl lipid A (MPL®)

The biologically active component of endotoxin is lipid-A whose structure is shown in Fig. 5. By removing specific phosphate groups as well as the sugar moieties, a detoxified derivative, Monophosphoril Lipid A (MPL®), has been obtained, which has retained immunostimulatory activities on dendritic cells (TLR4 agonist).

MPL® is marketed in Europe for allergy treatment because of its ability to enhance Th1 response to responses to allergens, hence suppressing the development of allergy and asthma. A range of ultra-short course MPL®-based subcutaneous allergy vaccines has been developed which requires the administration of only four injections before the start of the pollen season. Successful preliminary double-blind placebo controlled studies on these vaccines have already been conducted and, as a consequence, these products have been marketed since 1999 in Europe (nearly 70% in Germany) and other countries. Over 200,000 patients have used them to date [41].

As substantial exposure data are available from the named patient program (named patient products), product reviews have been carried out, at least in Canada [42] and New Zealand [43]. MPL® adjuvant is safe, well-tolerated and potent, and has been given to millions of individuals. MPL® is in fact already in use as adjuvant agent in human vaccines for cancer therapy (melanoma, cervical cancer, HER2-positive breast carcinoma, prostate cancer, colorectal carcinoma, MAGE-3-Expressing Cancers, STn-Expressing Carcinomas, MUC1-expressing cancers and RAS-expressing