

Cancer in North Cyprus: I. Current Status, An Overview

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This is the first of a two-part review dealing with cancer issues in North Cyprus (NC). Here we give an account of what is known about the cancer status of the island, which has been debated quite intensely over the years. From several independent reports, it is concluded that the epidemiology of cancer in NC has been steady around 200-230 per 100,000 for more than 20 years. This level is in line with the rest of Europe. Nevertheless, there are some potentially worrying signs. First, the "age-standardized rate" of some cancers (lung, skin, and liver) appears higher. Second, the "average age of incidence" is lower for breast and skin cancer in NC than in the rest of Europe. Relevant environmental factors of current interest that could contribute to these issues include the environmental levels of potentially carcinogenic heavy metals (e.g., arsenic, cadmium and lead) and the levels of vitamin D in the population. The particular case of the copper mines in the Lefke region is also covered. We conclude that (i) the overall cancer status of NC is broadly comparable to the rest of Europe, (ii) continuous monitoring of epidemiology is necessary, and (iii) research is needed into the possible cause(s) of cancer, especially environmental factors.

Keywords: Cancer, North Cyprus, epidemiology, heavy metal, vitamin D

INTRODUCTION

Cancer is now very much a part of modern life, its incidence increasing in line with life expectancy. At present, one in three men and one in three women in the Western world are expected to be diagnosed with some form of cancer during his/her lifetime (1). There were approximately 14 million new cases and 8.2 million cancer-related deaths globally in 2012 (2). According to the World Health Organization (WHO), these statistics are expected to rise by about 70% over the next two decades (3). As well as genetic disposition and age, worsening life styles (e.g., leading to obesity) and environmental impact are contributing to the problem globally. Importantly, since cancer is basically an epigenetic disease, it is malleable and can significantly be affected (promoted or suppressed) by external factors, especially environment, diet and lifestyle. Accordingly, cancers of the world can be divided into two groups. On the one hand, "cancers of affluence" (e.g., melanoma and cancers of thyroid and testis) are associated with developed countries including the Western world. On the other hand, "cancers of poverty" (e.g., Kaposi sarcoma and cancers of the liver, larynx, cervix and penis) tend to occur in less developed countries (4). Such distinction emphasizes the potential impact of socioeconomic status (e.g., employment, education and nutrition) on several cancers. In this overview, we give an account of the cancer status in North Cyprus (NC).

EPIDEMIOLOGY

In an initial study sponsored by the Cancer Research Foundation (CRF)/Kanser Araştırma Vakfı (KAV), Hincal et al. (5) evaluated the cancer incidence in NC in comparison with countries of North Europe (NE) and South Europe (SE). The latter included several Mediterranean countries where diet and lifestyle could be expected to be closer to the conditions in NC. This study covered the period 1990-2002. Two main statistical parameters were studied: age-standardized rate (ASR) and average age of incidence (AAI). On average, there were about 110 and 120 per 100,000 cases of cancer in males and females, respectively (total=230 per 100,000). We would urge some caution in this analysis, however, since in the absence of an official cancer registry and in spite of all the efforts made by Hincal et al. to ensure data quality, the ASR values in NC may have been underestimated somehow (5). Nevertheless, the three most serious cancers in NC (for which the ASR values were higher than either one or both SE and NE) were the following: lung (males), skin (both sexes) and liver (both sexes). The incidence of the following cancers appeared better than SE and/or NE: breast, prostate, stomach (both sexes), bladder (both sexes), colorectal (female), ovary, cervix and corpus. Two points are worthy of highlighting from these analyses. First, the values of AAI for breast cancer and skin cancer were lower than both SE and NE (for both sexes in the case of skin cancer). This would be independent of any possible underestimation of ASR values and could indicate genuinely that breast and skin cancers occur at an earlier age in NC compared to the rest of Europe. Therefore, there must

be some potential carcinogenic factor(s) in NC, most probably "external", i.e., environment and lifestyle. In the case of skin cancer, these would also include exposure to bright sunlight. Second, of the three most serious cancers, the high incidence of liver cancer was rather surprising since this is often associated with chronic hepatitis B/C viral infection and occurs most commonly in countries of the "third world" including many areas of Africa (6). Other risk factors include alcohol and arsenic (7). Nevertheless, all these three cancers are preventable.

The status of cancer in NC specifically in the year 2011 was more recently reported by Gokyigit and Demirdamar (8). The total incidence rate for all cancer cases was 201 per 100,000. This is close to the rate originally reported by Hincal et al. (5). Finally, an unofficial newspaper article reported 600 new cases of cancer in 2015 (9). Assuming the population of NC to be 300,000, this would mean 200 cases per 100,000, in line with the studies of Hincal et al. (5) and Gokyigit and Demirdamar (8). These three sets of data would indicate that the cancer incidence in NC has remained remarkably steady over the period 1990-2015. Furthermore, these rates would compare favorably with European countries where recently reported values vary in the range 224-338 per 100,000 (10). The five most common cancers reported by Gokyigit and Demirdamar (8) were breast, prostate, colorectal, thyroid, and lung. It was surprising that cancers of skin and liver were not prominent in this profile, unlike the report of Hincal et al. (5).

ENVIRONMENTAL ISSUES

Heavy Metals

Persistent heavy metal contamination in environment from both natural and anthropogenic sources can be of major concern as potential carcinogens. However, some heavy metals in the form of trace elements (e.g., selenium) at appropriate concentrations can have anticancer effects (11). Humans can be exposed to environmental heavy metals through water or by consuming vegetables and fruits that grow in contaminated soils. Plants cultivated in contaminated soil and groundwater can take up heavy metals through their roots and accumulate them in their edible parts. Analyses of heavy metals in soil and water of NC have been undertaken in continuing studies by CRF/KAV.

An initial partnership between CRF/KAV and Frederick Institute of Technology (FIT) in South Cyprus (SC), beginning in 2003, focused on selenium and covered different areas of Cyprus selected according to agricultural usage. A total of 481 composite soil samples were collected (225 samples from NC and 256 samples from SC) and analyzed in two independent laboratories. The average levels of selenium in the rainy season ranged between 0.00 and 0.26 ppm in NC and between 0.00 and 0.18 ppm in SC. On the other hand, in the dry season, the upper limits were observed to increase up to 0.41 ppm in NC and 0.44 ppm in SC. Taking 0.2 ppm as the optimum for deriving health benefits (e.g., by enhancing the immune system), as recommended by the U.S. Environmental Protection Agency (EPA), these areas can be accepted as fit for agriculture (12).

In 2005, the collaboration between CRF/KAV and FIT was extended to analyses of lead, cadmium, and arsenic in 260 composite soil samples (140 from NC and 120 from SC), covering Gü-

zelyurt, Bostancı, Yuvacık, Lefkoşa, Karpaz, Alevkayası, Kırmı, and Mesarya in NC and Dhali, Sotira, Omodos, Acheilia, Polis, and Evrychu in SC (13). The results were as follows:

1. Lead: The level was in the range 5.7-224.9 ppm in NC and 4.7-121.7 ppm in SC. Since the maximum allowable limit of lead in soil has been determined to be 400 ppm by the EPA, all areas in Cyprus seem to be safe with no risk to agriculture. However, we should stress that the concentrations of lead in soils taken from NC are noticeably higher than those taken from SC.

2. Cadmium: The cadmium levels found to range between 0.2 and 1.89 ppm in NC and 0.2 and 0.59 ppm in SC, with the highest value in Nicosia (1.89 ppm). These concentrations are partially above the maximum (1 ppm) level recommended by the EPA.

3. Arsenic: High levels of this heavy metal were found over the whole island. The arsenic concentrations ranged between 0.2 and 18.5 ppm in NC and 2.8 and 22.5 in SC, compared with the maximum safe limit of only 10 ppm. At present, the relative contributions of natural versus anthropogenic sources to these high levels are not known. Further work is required to determine the relative contributions of such sources and whether arsenic enters the food chain at any stage. Importantly, it would be possible to regulate environmental arsenic levels through specialized vegetation and/or using graphene (14, 15).

THE CASE OF THE COPPER MINES

The copper mines in the Lefke region of NC were exploited by Phoenicians and Romans over 2000 years ago. The deposits were re-activated around 1920 and this continued until 1974. Afterward, the entire site was made idle with only periodic plans for reclamation. Currently, there are approximately 10 million tons of contaminated tailings including potential carcinogenic heavy metals (16). It has been officially reported that the economic value of the tailings can cover around only half of the cost for reclamation (17). The major tailings pond, which will also be the major location for burying contaminated tailings, was constructed near the Gemikonağı artificial pond. Beneath this, a geomembrane was laid to stop seepage to underground water resources. Having underground wells providing potable water could increase the risk of contamination of the drinking water resources in the Lefke area. Consequently, new locations with improved geomembrane systems may be necessary. In fact, these tailings may not threaten just the Lefke region but could affect the entire island, even extending into the Mediterranean at large. Also, apart from copper, the tailings include the following chemicals: sodium cyanide, sulfuric acid, sodium sulfide, potassium ethyl/amyl xanthane, sodium ethyl/isopropyl xanthane, carbon disulfate, pine oil, and trichloroethylene (16). These additional chemicals originate from their use during the historic ore-processing methods to extract copper and gold (16).

Whether the defunct mines are a cause of cancer has been debated for a long time, without a clear conclusion. Interestingly, in the recent study of Gokyigit and Demirdamar (8), the highest cancer rate was found in the Güzelyurt-Lefke area. More generally, although copper is a micronutrient essential for normal life, with dozens of enzymes depending on it for their regular functioning, cancer cells can utilize the metal to promote their growth (18). In one study, drinking water containing 20 µM cop-

per (the maximum level allowed in municipal drinking water according to the EPA standards) did not induce any cancer but it did promote existing tumors (19). Also, interestingly, a copper-chelating drug, tetrathiomolybdate, was recently found to produce remarkable beneficial effects against breast cancer, including metastatic disease and recurrence, in humans and mice (20). Taken together, the available evidence would suggest that copper levels in the Lefke region should be monitored both in the environment (soil and water) and in the human body. The epidemiology of the region should also be monitored.

VITAMIN D

As already emphasized, cancer involves interactions between genes and "external" factors, especially environment and lifestyle. Balanced diet is essential for healthy living. Links between nutrition and cancer were highlighted many years ago and it was estimated that more than one third of all cancers might be attributable to dietary factors (21).

Vitamin D, a fat-soluble micronutrient, is an essential precursor to the steroid hormone calcitriol, the main physiological role of which is regulation of calcium and inorganic phosphate homeostasis for skeletal health (22). In humans, vitamin D is obtained mainly through synthesis in skin by exposure to sunlight and, to a lesser extent, by directly ingestion in certain foods or supplements. Unfortified foods that contain vitamin D naturally are limited mainly to oily fish, liver, and egg yolks (23). Even with optimal nutrition, however, up to 90% of our daily vitamin D requirement is met through cutaneous production driven by exposure to sunlight (24).

A negative association between vitamin D and colon cancer risk was noted originally by Garland and Garland (25). This has now been confirmed for many other cancers, including breast, prostate, and pancreatic cancers (26, 27). Many preclinical, epidemiological and clinical studies have been performed to understand the mechanism through which vitamin D may reduce cancer risk (28, 29). The primary mode of action of vitamin D is genomic whereby binding of 1.25(OH)₂D₃, the major metabolite of vitamin D, to the nuclear "vitamin D receptor", a transcription factor, leads to regulation of hundreds of genes in a cell-specific fashion. Net effects include strong suppression of cancer cell proliferation and differentiation (30). More recent evidence suggests, however, that vitamin D can also exert fast, non-genomic actions (31, 32).

An important advantage of vitamin D is that, unlike some supplements, its positive effects can occur even during cancer treatment without any apparent clash. This has been seen in a patient undergoing chemotherapy or biphosphonate treatment including reduction of some of the undesirable side effects of the treatments (33).

There has not been any systematic study of vitamin D levels in cancer patients (or healthy individuals) in NC. However, anecdotal evidence would suggest that the levels in cancer patients are often low (M.B.A. Djamgoz, unpublished observations). Interestingly, more than 80% of the Saudi Arabian population suffers from vitamin D deficiency (34). It would seem, therefore, that the input (sunlight) being available in plentiful is no guarantee that healthy levels of bodily vitamin D will be attained. If so, it

is possible that the metabolic pathway responsible for synthesizing vitamin D does not function normally in cancer patients or even in some healthy people (29, 35). Such abnormality may include polymorphisms in the vitamin D receptor (36).

CONCLUSION

In conclusion, although cancer incidence in NC is broadly in line with the rest of Europe, there are some negative signs that should be taken seriously. We would recommend that there should be continuous cancer awareness programs (targeting the population of all ages) and monitor of cancer cases. Research is also necessary to determine the cause(s) of those cancers for which ASR and/or All values appear relatively worse compared with SE and/or NE.

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