

THE ROLE OF FAMILIAL CANCERS IN CANCER EPIDEMIOLOGY

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Cancer is genetic disease which occurs due to modification of the normal cell DNA as a result of exposure to physical, chemical, or biological factors encountered in the surrounding environment and/or appearing within the cell itself. Modification of a normal cell DNA is called mutation. For example, such a modification (mutation) may cause skin cancer by damaging the structure and function of certain significant genes such as the p53 tumor suppressor gene due to ultraviolet B radiation (de Gruijl, 1999). Such mutations, which cause cancer as seen in the case of skin cancer, can either appear due to various environmental effects or be transmitted to the child from his mother or father. Contributions of environmental or hereditary factors to occurrence of cancer differ according to the type of the cancer and the surrounding environment. While there are types of cancer which occur solely due to environmental factors, there are also types of cancer which appear due to an anomaly of a single gene. For example, almost all liver cancers develop due to exposure to biological factors such as hepatic viruses (HBV and HCV) or chemical factors such as aflatoxin (Bruix et al, 2003). No genetic factor, independently significant for the development of liver cancers, has been evidenced. On the other hand, 5-10% of breast and large intestine cancers, which are among the most frequent cancers, are accepted to occur due to mutations in well-defined genes (Nagy et al, 2004). The probability of those who have such high penetrance (rate of occurrence of the disease in those having the relevant disease gene) genes to develop cancer throughout their lives is almost 100%, independently from environmental factors. On the other hand, again in one group of breast and large intestine-rectum cancers, despite variations among the societies analyzed and publications, the number of cases with familial cluster is reported to be 15-20% (Nagy et al, 2004). It is accepted that

these familial cancers occur as a result of the mutual interaction of low penetrance genes or low penetration genes and environmental factors. In these types of cancer without familial cluster, a single mutation in a gene is not sufficient for the development of cancer; supplementary mutations and/or environmental factors are also necessary for cancer development in an individual (Balmain et al, 2003, Phoroah et al, 2002).

The genetic structure of an individual can produce direct susceptibility to cancer development and it is also effective in the response given by the individual to the environmental factors. In other words, the genetic structure is a determining factor in either more susceptibility or more resistance of an individual to the harmful effects of the environmental factors. It seems that the relationship between the environment and genes is a very complex relationship in formation of cancers, and environmental factors and genetic susceptibilities should be analyzed together for the purpose of development of a cancer policy. However, in Turkey, the analysis of the role of genetic susceptibilities in cancers has been restricted to the research of the universities so far, and the findings could not be obtained at the societal level. The main reasons of this may be briefed as follows:

1- Regional risk maps of the regions that pose risks of cancer are not available for Turkey.

2- It is a common belief that the control of environmental factors identified in cancer control may produce more effective solutions than the control of genetic causes.

3- The genetic bases of cancer and genetic transformations that cause various cancers have started to be illuminated within the last 10-15 years, but all cancer susceptibility or resistance genes have not been identified yet.

4- High costs of genetic studies result in negligence of the topic of genetic susceptibilities.

5- Cancer registration systems are far from detecting familial/regional clusters. Registration system designed for the purpose of detecting such clusters, in turn, are not preferred for the ethical problems they bring along

6- The reliability of the statistical analyses used in molecular genetic studies on genetic susceptibilities is highly influenced by gene structures identified by ethnic characteristics. In Turkey, the inability to obtain ethnic information in a healthy way reduces the reliability of these analyses despite their high costs.

The negligence of the topic of genetic susceptibilities owing to all these reasons results in a decline in the effectiveness of cancer control programs, a meaningless panic towards environmental factors in regions with certain cancer clusters, failure to control environmental factors effectively, and failure to provide preventive medicine services such as

early diagnosis, pre-symptomatic treatment and individual-specific treatment, which are provided in various diseases thanks to genetic studies in cancer.

In consideration of these aspects, a pilot study, “**National Work Group on Genetically Transmitted Cancers**”, has been launched with the participation of various universities under the coordination of the Ministry of Health, Department of Cancer Control. This group, first, established connections with primary care services and conducted a study to roughly determine the regions where cancer cases with familial cluster are observed. In this study, the following criteria have been taken into consideration:

- 1- Accumulation of a single type of cancer in the same region/same family
- 2- Clustering of different types of cancers in the same family
- 3- At least in one of the cancer cases, occurrence of the cancer far before the expected age.

According to the records of the Department of Cancer Control, in Turkey, cancer incidences differentiate by regions. Among these regions, the regions most studied on are Tuzköy and Karain villages of Göreme. In these regions, it is known that 70% of cancer deaths are due to mesothelioma. Although the zeolite minerals existing in the surrounding environment have been held responsible for the etiology of these cases (Barış et al, 1987), recent studies conducted in the region show that familial genetic susceptibility may also have a role in occurrence of this cancer (Roushdy-Hammady et al, 2001; Carbone et al. 2007). More detailed information is provided by Dr. Salih Emri in the chapter on the mesothelioma problem in this book. In Turkey, familial aggregation is observed in lung cancers also in regions other than Tuzköy, especially in certain mountain villages in Taurus Mountains. Increase in cancers in these regions should be analyzed in consideration of the genetics-environment relationship.

In cancers, a second indication of genetic susceptibility is the occurrence of different types of cancers in the same family, village or in individuals of a common ethnic origin. Upon such notifications, it is appropriate to conduct detailed family tree analyses along with studies on environmental factors. In familial cancers, the syndromes of cancer susceptibility are significant. The Li-Freumani syndrome, wherein cancers of different organs such as soft tissue and bone sarcomas, breast cancer, leukemia, melanoma, colon, pancreas and adrenal tissue cancers that appear at an early age and transmitted by a dominant effective gene are aggregated in the same family, is an example of this group of cancers (Li et al.1988). In most of these syndromes, cancer occurs due to a defect in a single gene, independently from the environment. However, there is almost no information available on how environmental factors change genetic expressions. In countries with an average of early age of marriage and a high birth rate, like Turkey, it is obvious that families with cancer susceptibility syndrome can well change the figures of regional cancers. As the contribution of genetic-environmental factors cannot be identified

unless a detailed familial analysis is conducted, inhabitants of these regions experience a meaningless panic. This situation is nurtured by fears lacking any scientific support such as that cancer might be a contaminant, which may sometimes result in rejection of trading with these villages.

In Turkey, upon a notification made from Zonguldak to the Department of Cancer Control, a detailed field research has been conducted in Gökçeler region of Zonguldak. The research was conducted with the participation of researchers from Bilkent, Hacettepe, ODTÜ (Middle East Technical University), and Anatolian universities and the MTA (Mineral Research and Exploration Institute) under the control of the Department of Cancer Control and with research support from the Terry Fox Foundation. It is reported that pancreas cancer, cancers of stomach and female genital organs, polyposia coli and lung cancers are aggregated and very rare cancers such as osteosarcoma are observed in the region. Detailed pedigree analyses have shown that consanguineous marriage is frequent in the region. The analysis of a family of 85 members of the same ancestor has suggested that cancers are observed in the same family and in individuals of the same family who have gone to other villages. The index case is a female patient under the age 20 diagnosed with osteosarcoma and the father of the patient was diagnosed with pancreas cancer and lost when he was 41. A brother of the patient was diagnosed with polyposia coli and is under monitoring. An aunt and three uncles of the patient were lost at an early age due to cancers of different organs. Deaths due to cancers of stomach, lung, and female genital organs have been frequently observed also in other small family trees in connection with this family tree. Although the distribution of cancers in the family tree suggests an autosomal dominant character, frequent consanguineous marriages create difficulty in assessment of the possible genetic pattern of the diseases. Appearance of cancer types such as sarcoma, colon cancer, and pancreas cancer in each generation, early start age and aggressive prognosis are in line with the Li-Fraumeni syndrome criteria (Varley et al, 1997). The *p53* gene, which is pointed out as a factor in 80% of this syndrome, was scanned for mutation in the index patient, but no mutant modification that might be the factor of the diseases has been observed. In this syndrome, mutations in the *CHEK2* gene have been reported in a smaller number of cases, yet studies on this gene have not been completed yet (Lee et al. 2001).

In the region, studies on environmental geology have also been completed (Kadir et al, 2007 – in print). Samples of rock, soil, water, air, plaster/concrete, and coal were collected from the region and they were subjected to thin section, bright section, XRD, scanning electron microscopy and geochemistry studies. In micromorphologic analyses, mordenite and chrysotile are found in settlement areas. Both are small minerals that can be inhaled into the body. Effects of both minerals on cancer development are still subject to discussions. As a result of these studies, the gene responsible for the cancers observed in the region could

not be identified on the basis of the family tree information and cancer types aggregated in the family; yet, it is thought that these cancers have a genetic cause and environmental factors do not have primary effect on the appearance of the diseases.

Other than these two examples of familial cancer susceptibility, interesting cancer clusters are observed in various regions of Turkey. The lymphoma aggregation observed in rural areas of Bingöl province also requires an analysis of genetic factors, in terms of familial cancer clusters, and environmental factors.

Continuation of these studies initiated under the Department of Cancer Control will bring different universities and different disciplines together for the same goal and will result in environmental and genetic risk mapping studies, which is an imperative for Turkey.

References:

1. Balmain A, Gray J, Ponder B. The genetics and genomics of cancer. *Nat Genet.* 2003; 33:238-44.
2. Barış İ, Simonato L, Artvinli M, Pooley F, Saracci R, Skidmore J, Wagner C. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: a four-year study in the Cappadocian region of Turkey. *Int J Cancer.* 1987; 39:10-7
3. Bruix J, Boix L, Sala M, Llovet JM. Focus on hepatocellular carcinoma. *Cancer Cell.* 2004; 5:215-9.
4. Carbone M, Emri S, Dogan AU, Steele I, Tuncer M, Pass HI, Baris YI. A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes. *Nat Rev Cancer.* 2007; 7:147-54.
5. Gruijl FR. Skin cancer and solar UV radiation. *Eur J Cancer.* 1999; 35:2003-9
6. Kadir S, Önen-Hall AP, Aydın SN, Yakıcıer C, Akarsu NA, Tuncer M. Environmental Effect and Genetic Influence: A Regional Cancer Predisposition Survey in the Zonguldak Region of Northwest Turkey, *Environmental Geology.* 2007 (baskıda)
7. Lee SB, Kim SH, Bell DW, Wahrer DC, Schiripo TA, Jorczak MM, Sgroi DC, Garber JE, Li FP, Nichols KE, Varley JM, Godwin AK, Shannon KM, Harlow E, Haber DA. Destabilization of CHK2 by a missense mutation associated with Li-Fraumeni Syndrome. *Cancer Res.* 2001; 61:8062-7.
8. Li, FP, Fraumeni JR.Jr, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA, Miller RW. A cancer family syndrome in twenty-four kindreds. *Cancer Research,* 1988; 48: 5358-5362
9. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. *Oncogene.* 2004; 23: 6445-70
10. Pharoah PD, Antoniou A, Bobrow M, Zimmern RL, Easton DF, Ponder BA. Polygenic susceptibility to breast cancer and implications for prevention. *Nat Genet.* 2002; 31:33-6
11. Roushdy-Hammady I, Siegel J, Emri S, Testa JR, Carbone M. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. *Lancet.* 2001; 357: 444-5.
12. Varley JM, McGown G, Thorncroft M, Santibanez-Koref MF, Kelsey AM, Tricker KJ, Evans DG, Birch JM. Germ-line mutations of TP53 in Li-Fraumeni families: an extended study of 39 families. *Cancer Res.* 1997;57:3245-52