2017 International Nuclear Atlantic Conference - INAC 2017
Belo Horizonte, MG, Brazil, October 22-27, 2017
ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR – ABEN

Agência Brasileira do ISBN
ISBN 978-85-99141-07-6
9 788599 141076

STUDY ON FATAL AND NONFATAL CANCER CASES OCCURED IN DIFFERENT REGIONS OF SÃO PAULO CITY

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ABSTRACT

São Paulo city has presented an increasing change regarding the causes of mortality. An overview of the distribution and types of cancer in different populations can be obtained from official databases that collect general data de Base Populacional (RCBP) provides data description of patients and monitors the profile of cancer from patients. The system aims to know the incidence of malignant neoplasm. The database named Registros de Câncer incidence in a given population. The RCBP of the city of São Paulo is coordinated by the Department of Epidemiology of the School of Public Health, University of São Paulo .The RCBP allows the assessment of data from all areas of São Paulo. The aim of this paper is to provide a review of data about the cases of fatal and nonfatal cancer in several areas of the city of São Paulo (Midwest, East, North, Southeast and South) in order to establish a comparison among the occurrences of the disease in those areas. The review will be an efficient tool to identify the profile of cancer cases in the city of São Paulo, mainly in the areas where most hospitals, which provide therapy and imaging services that use radiation, are located. Based on the data review a future epidemiological study may be conducted seeking to identify the main types of cancer that may be directly or indirectly related to radiation such as leukemia, thyroid, breast, and bone cancer. The existence of several other risk factors that may interfere with the development of any type of cancer, such as individual lifestyle and genetic predisposition must be considered.

1. INTRODUCTION

According to the World Health Organization (WHO), by the year 2030, there will be around 27 million cases of cancer, with 17 million deaths, and 75 million people annually living with cancer [1]. In Brazil, the Brazilian Cancer Institute (INCA) has estimated approximately 600 thousand new cases of cancer for the biennium 2016-2017 [1]. Currently, it represents the third most important cause of death among Brazilian population [2]. Moreover, it is considered one of the most common health problems in the city of São Paulo [3].

Epidemiological studies of cancer have been fundamental for demonstrating the several risk factors related to the carcinogenicity of malignant neoplasms, important for establishing public health policies and for assisting the planning of cancer prevention and control actions [4]. In Brazil, the Population-Based Cancer Registries (PBCR) database provides information about the impact of cancer in communities, being an important tool to understand the risk factors and establish new estimates for cancer cases [5]. The Hospital Registry of Cancer (RHC) is responsible for collecting, storing, processing, analyzing, and disseminating the information of patients diagnosed with cancer, who are treated at a Hospital Unit (HU) [6]. The PBCR, RHC and the Single Information System on Mortality (SIM) of the Department of Informatics of the Brazilian National Health System (DataSUS) have been used in epidemiological investigations and in the development of cancer research [1].

1.1. Theory of radiation-induced cancer

The studies confirmed that exposure to ionizing radiation may increase the risk of cancer induction in several species and this risk may change according to the dose of radiation received, to genetic predisposition and to the sensitivity of the exposed tissue [7; 9]. It is well known that exposure to radiation can affects not only exposed people, but also the entire environment around and nearby populations if the radiation is used of form incorrect, i.e., without following the radiological protection protocols. Therefore, it is important to establish a relationship between exposure to ionizing radiation and the occurrence of fatal and nonfatal cancer, especially in places and institutions that perform nuclear and radiological applications [9].

The Occupationally Exposed Persons (OEP), who are the individuals working in the nuclear industry or in laboratories and hospital around equipment that emits radiation are constantly exposed to low doses of ionizing radiation [9; 10]. According to INCA, the peculiarity of carcinogenesis related to occupational exposure is the great potential of existing prevention [6].

To ensure an adequate level of individual radiological protection for each OEP, an effective dose restriction value has been established taking into account the uncertainties associated with it, regarding any source or facility under regulatory control. The level of investigation for individual monitoring of OEP for the effective dose is 6 milli Sievert (mSv) per year or 1 mSv in any month and the effective annual average limit dose in 5 consecutive years is 20 mSv, having a dose limit of 50 mSv in one year [10].

Information suggests that steam cells or early progenitor cells are more predisposed to carcinogenic effects of radiation exposure [7]. Due to this information, pregnant women who are occupationally exposed should be monitored since the reporting of pregnancy to ensure the fetus will not receive an effective dose greater than 1 mSv during the gestation period. Moreover, individuals under the age of 16 years may not be subject to occupational exposures [10].

Currently, medical surveillance has used dosimetry that makes the physical control of the operators for the prevention of possible stochastic effects of radiation [9]. Although this method is effective to reveal any accidental overexposure, it does not provide information on the risk of exposure to low levels of radiation for prolonged periods. For this reason, agencies and organizations involved in important radioprotection programs have emphasized the need

for new preventive initiatives for the surveillance of workers exposed to ionizing radiation [12; 13; 14].

The levels of radiation exposure due to medical uses have also increased, especially in developed countries [14]. This is because of the increasing use of diagnostic methods and intervention procedures that use radioactive sources such as computed tomography (CT), mammography, angiography, among others. The estimated annual effective dose for all diagnostic methods that use radiation were 1.2 mSv per person in the period from 1991 to 1996, and from 1985 to 1990 it was 1.0 mSv per person. Due to medical procedures US citizens received in 2006 a collective effective dose 7.3 times higher than in the early 1980s, as shown in Fig. 1 [15].

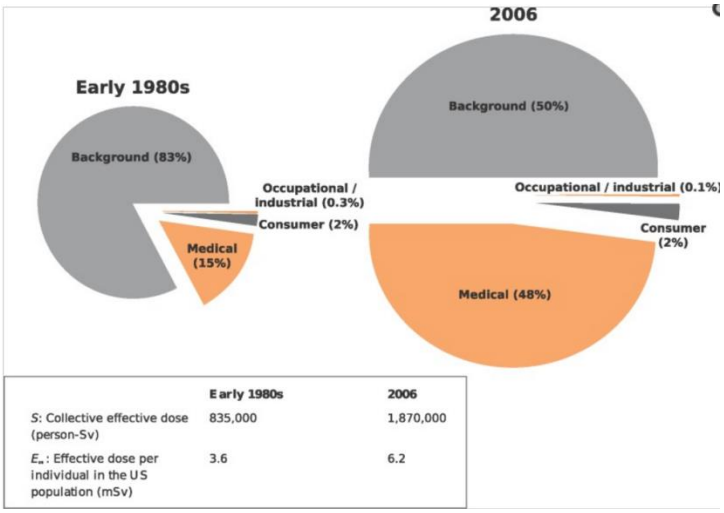

Figure 1: Effective collective dose in the US in the early 1980s compared to 2006.

The biological effects caused by exposure to ionizing radiation are mainly due to an indirect action of radiation through its interaction with the water molecule. In humans, this occurs because water is present in 70% to 80% of the body and because water is a universal solvent where several chemical reactions occur [25].

By interacting with biological tissues, X-rays, gamma, and neutrons can excite water molecules or cause free radicals to form that are highly reactive and can interfere with the metabolism of proteins, lipids, and carbohydrates. Radiation can also act on DNA through the action of by-products of water radiolysis, which can cause simple breaks that are quickly and efficiently repaired or double breaks in the DNA strand that can cause chromosomal abnormalities and genetic mutations [26]. In addition, the release of hydrogen protons reduces the pH and can lead to protein denaturation and cell death [27].

The break in the double strand of DNA is an important event for the formation of chromosomal changes, which if not repaired, can induce genomic instability, cancer, and apoptosis [28]. For a few years chromosomal changes have been used as biological dosimeters and have proven to be a fairly reliable parameter for the assessment of radiation-induced damage in humans, even in low-dose accidents. Previous studies performed with OEP, who worked in hospitals and were exposed to low doses of radiation for a prolonged

period, revealed an increase in the basal level of OEP chromosomal aberrations when compared to the control population [29].

Currently, the carcinogenic process is considered both a genetic and an epigenetic process. In both cases it has several steps resulting in the damage of a single cell, which will cause an abnormal phenotype, resulting in increased growth and altered functionality [31]. Cells that were not directly irradiated can display cells around them that have undergone some exposure to radiation; this is due to the spectator effect that demonstrates the possible induction of tumor formation through epigenetic processes [30].

X-ray and gamma were classified as Group I by the International Agency for Research on Cancer (IARC), demonstrating that there is sufficient epidemiological evidence for carcinogenicity in biological tissues [9]. A study in mice and rats found that the tissues that are most sensitive to radiation are the hematopoietic, mammary, thyroid and bone tissue. It was also noted that individuals exposed to high doses of ionizing radiation have a five-fold increased risk for developing leukemia and twice the risk of developing breast cancer, especially if this exposure occurred before menopause [7].

1.2. Literature review

Leukemia occurs due to a sequence of acquired genetic changes that result in an anomalous and genetically unstable clone, which may cause clonal and maturation defects in hematopoietic progenitor cells [17]. There was an increased incidence of leukemia, especially myeloid leukemia, in survivors of the Hiroshima and Nagasaki bombs and it was also observed that the risk was higher when exposure occurred in childhood or puberty [8].

Previous studies have reported that intrauterine exposure to X-rays increases the risk of developing childhood leukemia by 40% [18]. It was observed that the risk of leukemia death among radiologist physicians was nine to ten times higher than among physicians who are not occupationally exposed [19]. This finding was supported by another research where it was reported that in the period from 1948 to 1961 there was a significant increase in the number of leukemia deaths among American radiologists [20].
In 2016 a total of 10,070 new cases of leukemia were expected in Brazil, with 5,540 in men and 4,530 in women [1]. It was estimated that in 2013 a total of 6,316 leukemia deaths occurred, being 3,439 men and 2,877 women [32].
Breast cancer is considered a cancer of multifactorial origin and may involve biological and endocrine factors, exposure to ionizing radiation and lifestyle. It is the second most common type of neoplasm and the largest cause of cancer death in women worldwide. In Brazil it represents about 25% of new cases of cancer each year [1]. It was estimated by INCA that there would be 57,960 new cases of breast cancer in 2016 [32].

Epidemiological studies indicate an increase in the incidence of breast cancer in survivors of atomic bombs, demonstrating that breast tissue is highly sensitive to radiation [20]. It is well established that exposure before or during puberty raises the risk of breast cancer, as demonstrated in a study comparing women who were constantly irradiated in childhood with women who were little exposed. The study concluded that exposure of breast tissue in childhood and puberty may increase the risk of developing breast cancer in later life. The results show that the increase in risk only became apparent thirty years after the constant exposure to low doses of radiation. Those results reported that this fact occurs due to the long

period of latency of the disease [21]. Another study conducted with women chronically exposed to ionizing radiation before the age of 20 – due to the use of X-rays in the diagnosis of scoliosis – demonstrated an increased risk of developing breast cancer. The average dose received by the mammary tissue after 25 exposures were 108 mSv but the risk was also significant even after receiving doses between 10 and 90 mSv [16]. An increase in the incidence of breast cancer has been reported in both Canada and the United States in patients undergoing fluoroscopy and chest X-rays for the diagnosis and treatment of diseases [33].

The best-established risk factor for thyroid cancer is the exposure to ionizing radiation that may be due to treatment, diagnosis, environmental factor or occupational risk, and when started before the age of five, it seems to have a greater carcinogenic effect [22]. This risk factor is reported in studies carried out after the atomic bombs exploded in Japan and after the Chernobyl accident, where there was an increase in vulnerability to radiation in children and in female. These studies concluded that the cases of thyroid cancer in women were almost five times the number of cases among men [1; 34].

MicroRNAs are small RNAs that regulate the gene expression of plants and animals. They are responsible for regulating biological processes such as cell differentiation, proliferation and apoptosis, and also for participating in pathological processes such as the development of cancer. There is evidence that microRNAs are part of carcinogenesis, especially of thyroid cancer, and that their levels of expression may vary after irradiation [23].

INCA estimated that in 2016 there would be 5,870 new cases of thyroid cancer in women and 1,090 cases in men; thus approximately 84% of the cases would affect the female, confirming that women are more affected by the disease [1].

Ewing's tumors are a type of cancer of primitive neuroectodermal cells, which are composed of embryonic cells that have migrated from the neural crest, and depending on their degree of differentiation are called Ewing's Sarcoma or Peripheral Primitive Neuroectodermal Tumor (PPNET). They can affect bones and soft tissues, but the most common type is Ewing's sarcoma that mainly affects long and flat bones [1].

The epidemiological information on the irradiation relationship and the carcinogenic effects in Ewing's tumor cases are taken from studies of exposed people due to atomic bombs, medical procedures, environmental and occupational exposures [9].

Two studies reported, respectively, eleven and two cases of bone sarcoma, where the main cause considered was the treatment of cervical cancer with radiotherapy, showing a relation between the treatment using radioactive sources and the increased incidence of bone cancer. They also concluded that Ewing's tumor is more common in women, since they are subject to more frequently to pelvic radiation for diagnostic methods and for treatments of other diseases [24; 11].

Based on this scenario, it is essential to continue collecting data and follow-up of new and old cases of malignant neoplasms in order to obtain further information for future epidemiological studies [6].

The aim of this paper is to provide a review of data about the cases of fatal and nonfatal cancer in several areas of the city of São Paulo (Midwest, East, North, Southeast and South) in order to establish a comparison among the occurrences of the disease in those areas.

The review will be an efficient tool to identify the profile of cancer cases in the city of São Paulo, mainly in the areas where most hospitals, which provide therapy and imaging services that use radiation, are located. Based on the data review a future epidemiological study may be developed seeking to identify the main types of cancer that may be directly or indirectly related to radiation such as leukemia, thyroid, breast, and bone cancer.

The existence of several other risk factors that may interfere with the development of any type of cancer, such as individual lifestyle and genetic predisposition must be considered.

2. METHODOLOGY

This is study on cases of fatal and nonfatal cancer occurred in different regions of São Paulo city was conducted to assist the identification of the scenario of the disease in the city of São Paulo by quantifying the incidence and mortality in each area of the city and analyzing the incidence of specific types of cancer (that can be radiation-induced) in all areas including the central area where most hospitals, which provide therapy and imaging services that use radiation, are located. The databases used for this study will be briefly described in the following section.

TabNet is a generic application for tabulation available in public domain. It allows a fast tabular data arrangement under the request of user. This application was developed by DATASUS, the Unified Health System Information Technology Department, for the purpose of generating information from the database of the Unified Health System (SUS) [6].

2.1. Data Source

The data used to perform this work were collected at the RCBP-SP, which is coordinated by the Department of Epidemiology of the Faculty of Public Health of the University of São Paulo. A person may be registered several times depending on the occurrence of new malignant tumor in different topographies. The data are actively collected by using standardized data form in more than 300 sources: general and special hospitals, clinics, cancer prevention clinics, institutions of oncology, institutions of chemotherapy and/or radiotherapy, pathological anatomy laboratories, nursing homes and institutions of autopsy [7, 8].

The information is complemented by data associated with the death certificates provided by the Mortality Information Improvement Program of São Paulo city (PRO-AIM) and the State Institute of Data Analysis System (SEADE). The PRO-AIM processes the certificates of the deaths occurred in São Paulo city. The data source is the Mortality Information System (SIM) [7, 8].

2.2. Period and Study Population

The data analyzed here correspond to a period that covers all the available years in all health information systems included in this study.

Reported cases of cancer by sex and by year from 2006 to 2014, as presented in this work, refer to the entire city of São Paulo.

The absolute numbers of deaths due to neoplasms between 2006 and 2014, as presented below, correspond to different Regional Health Coordination Units (CRS) of São Paulo city, which are responsible for the coordination, articulation, and organization of the loco-regional health system, besides the matching of the plans, programs and projects of the Regional Health Departments (DRS), in accordance with the policies and guidelines of the Health Department of São Paulo State (SES/SP) and with the available resources. In Table 1, the boroughs of São Paulo city assessed in this study are presented with the respective Health Technical Supervisions (STS) [7-8].

The main purpose of evaluating all the boroughs pertaining to São Paulo city was the identification of incidence and mortality of all types of cancer in the city of São Paulo in a given period.

Table 1: Regional Health Coordination Units of São Paulo city and the respective Health Technical Supervisions [7, 8]

Regional Health Coordination Units (CRS)	Health Technical Supervision (STS)
Central	**Sé** (Bela Vista; Bom Retiro; Cambuci; Consolação; Liberdade; República; Santa Cecília; Sé)
East	**Cidade Tiradentes** (Cidade Tiradentes) **Ermelino Matarazzo** (Ermelino Matarazzo; Ponte Rasa) **São Miguel** (Jardim Helena; São Miguel; Vila Jacuí) **Guaianases** (Guaianases; Lajeado) **Itaim Paulista** (Itaim Paulista; Vila Curuça) **Itaquera** (Cidade Líder; Itaquera; José Bonifácio; Parque do Carmo) **São Mateus** (Iguatemi, São Mateus; São Rafael)
North	**Casa Verde/Cachoeirinha**(Cachoeirinha; Casa Verde; Limão) **Freguesia/Brasilândia** (Freguesia do Ó; Brasilândia) **Pirituba** (Jaraguá; Pirituba; São Domingos) **Perus** (Anhanguera; Perus) **Santana/Jaçanã** (Santana; Tucuruvi; Mandaqui; Jaçanã; Tremembé) **Vila Maria/Vila Guilherme** (Vila Guilherme; Vila Maria; Vila Medeiros)
West	**Butantã** (Butantã; Rio Pequeno; Raposo Tavares; Vila Sônia; Morumbi) **Lapa** (Barra Funda; Jaguara; Jaguaré; Perdizes; Lapa; Vila Leopoldina)

Southeast	**Ipiranga** (Cursino; Ipiranga; Sacomã) **Moóca/Aricanduva** (Água Rasa; Pari; Mooca; Brás; Belém; Tatuapé; Carrão; Aricanduva; Vila Formosa) **Penha** (Artur Alvim; Cangaíba; Penha) **Vila Mariana/Jabaquara** (Moema; Saúde; Vila Mariana; Jabaquara) **Vila Prudente/Sapopemba** (Vila Prudente; São Lucas; Sapopemba)
South	**Campo Limpo** (Campo Limpo; Capão Redondo; Vila Andrade) **Capela do Socorro** (Cidade Dutra; Grajaú; Socorro) **M'Boi Mirim** (Jardim Ângela; Jardim São Luís) **Parelheiros** (Marsilac; Parelheiros) **Santo Amaro/Cidade Ademar** (Campo Belo; Campo Grande; Santo Amaro; Cidade Ademar; Pedreira)

2.3 The Description of Variables for Data Tabulation

In order to obtain the number of reported cases of cancer (all kinds of cancer: both fatal and nonfatal), by sex and by year, between 2006 and 2014, in São Paulo city, the following variables were considered [7-8]:

- **Year:** Year of diagnostic of the registered tumor;
- **Gender:** Gender of the patient whose tumor was registered – male or female;
- **Topography 3dig:** Primary Location of registered tumor according to the International Classification of Diseases for Oncology - ICD-O, 3rd edition, 3 digits;
- **Topography 4dig:** Primary location of the registered tumor according to the International Classification of Diseases for Oncology - ICD-O, 3rd edition, 4 digits;
- **Morphology:** Characterization of the histological diagnosis of the registered tumor in accordance with the International Classification of Diseases for Oncology - CID-O, 3rd edition;
- **Age group**: Patient's age whose tumor was registered, between 1 and 80 years only;

For the absolute numbers of deaths due to neoplasms for different CRS of São Paulo city between 2006 and 2014, the following variables were considered [7,8]:

- **Place (of occurrence) of death** (available in TabNet databases from 2001, looking for changes in the categorization of this variable in the death certificate in the current year): Hospitals, other health facilities, home, highway and others;
- **Medical institutions where death occurred**: Administrative Ward of Residence and Borough of Residence of the dead. The city of São Paulo is subdivided into 96 administrative wards. A borough (31) consists of several wards;
- **Month and year of death**: Month and year of occurrence of death (data available from 1996);
- **Causes of death classified in accordance with the International Classification of Diseases** (WHO): The 10th Revision of the Classification - ICD-10 became effective since 1996;

- **Group of age of the dead**: between 1 and 80 years only;
- **Gender of the dead:** Male or Female;
- **Race/Complexion** (or skin color) (variable introduced in the death certificate in 1997 and available in database of the PRO-AIM from 1998): White, black, yellow, pale and indigenous;
- **Education level** (time in years of complete formal education**;** available in TabNet databases from 2001, aiming at changes in the categorization of this variable in the death certificate in the current year**):** None, from 1 to 3, from 4 to 7, from 8 to 11; from 12 and upward is not considered.

3. RESULTS AND DISCUSSIONS

Figure 2 shows the notified cases of fatal and nonfatal cancers in São Paulo city according to gender (male or female) and year, from 2006 to 2014.

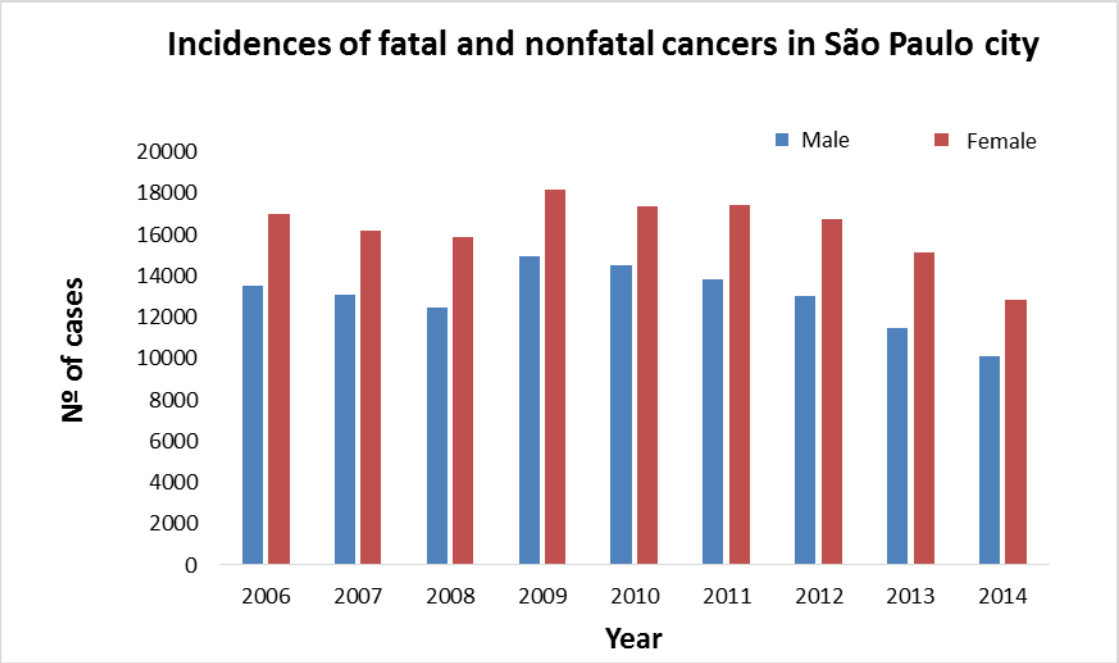

Figure 2: **Reported cases of cancer in São Paulo city from 2006 to 2014 according to gender and year [7, 8].**

The number of cases of different types of cancer reported between 2006 and 2014 corresponds approximately 396.450 in São Paulo, in relation to a population of approximately 11,870,657 inhabitants, this represents a rate of incidence 3.34%, being most of the cases related to female these data refer to the incidence of cancer caused by different risk factors involved in carcinogenesis and reflect the magnitude of this disease in the city.

Figure 3 shows the number of deaths of the inhabitants of different boroughs of São Paulo due to neoplasm from 2006 to 2014. It can be observed high mortality rate due to different types of cancer, where approximately 111,960 deaths occurred, against 559,800 deaths occurred by other causes. It represents a rate of mortality of approximately 20.0% caused by cancer, being most of the cases related to central region with approximately 6,464 deaths occurred.

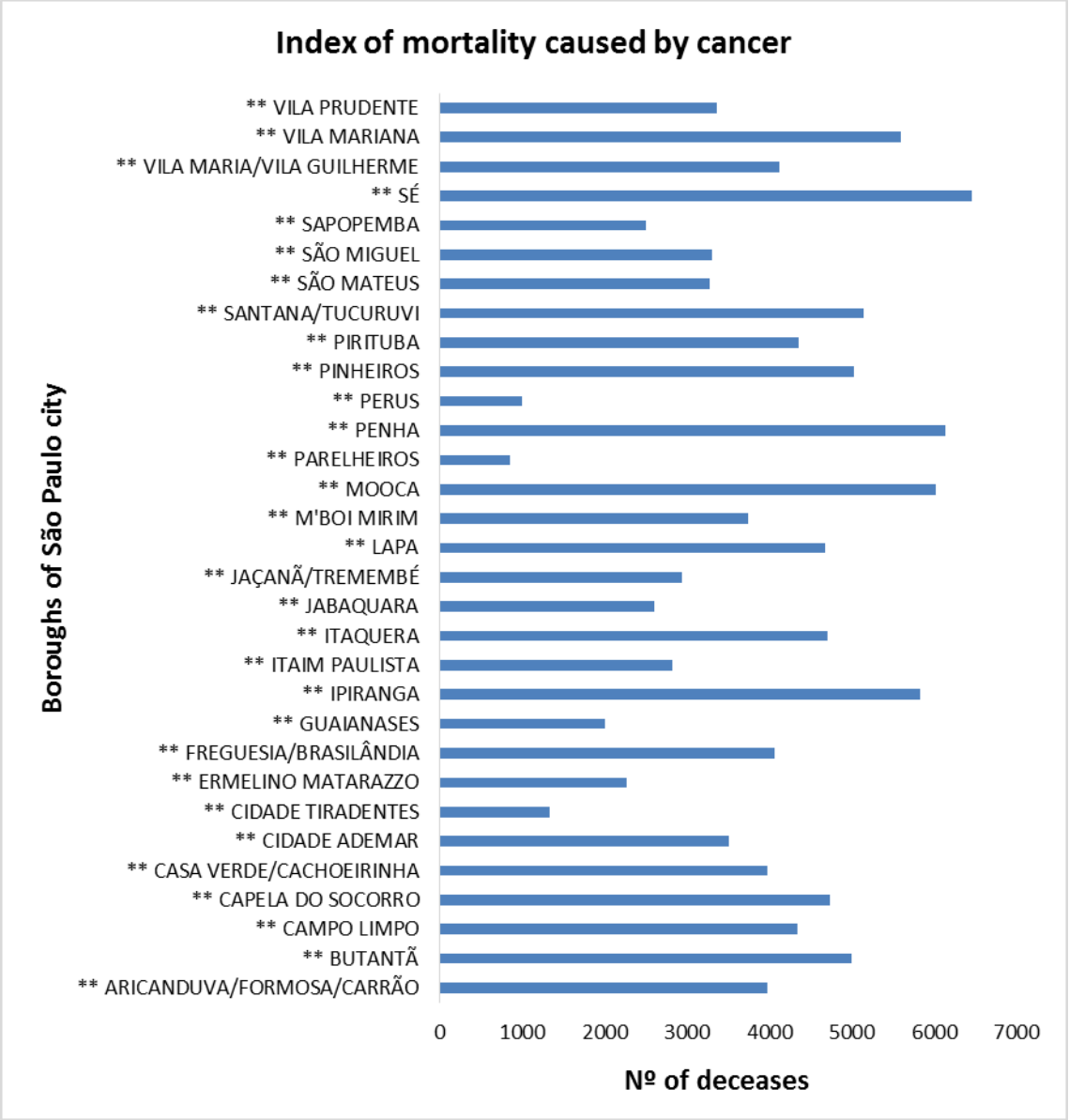

Figure 3: Notified cases of cancer in São Paulo city from 2006 to 2014 by sex and by year [7, 8].

Table 2 shows the main types of radiation-induced cancer, (which may also be related to others risk factors): bone, breast, thyroid and leukemia. Those data were collected in all areas of São Paulo. The central area has lower incidence of those types of cancer.

Table 2: Regional Health Coordination Units of São Paulo city and the respective Health Technical Supervisions [7, 8]

CRS/Cancer type	Bone	Breast	Thyroid	Leukemia
Central	27	633	24	46
East	122	1732	64	127
North	119	2194	88	156
West	60	1380	52	105
Southeast	156	3268	125	228
South	133	1750	55	137

4. CONCLUSIONS

Based on the data review from TabNet it was possible to identify the incidence and mortality of different types of cancer in the city of São Paulo. The study also provided information about the main types of cancer that may result either from lifestyle, genetic predisposition or radiation exposition.

This review will be an efficient tool to identify the profile of cancer cases in the city of São Paulo, mainly in the areas where most hospitals, which provide therapy and imaging services that use radiation, are located. Based on this data review a future epidemiological study may be conducted seeking to identify the main types of cancer that may be directly or indirectly related to radiation such as leukemia, thyroid, breast, and bone cancer.

ACKNOWLEDGMENTS

The authors would like to thank ELETROBRAS ELETRONUCLEAR/CAPES and the Centro de Engenharia Nuclear of IPEN for the financial support.

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