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RESEARCH ARTICLE

Incidence of Cancer Due to Exposure to Ionizing Radiation: A Cohort of Nuclear Sector Workers in the City of São Paulo

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ABSTRACT

Objective: To compare cancer incidence between workers exposed to ionizing radiation in an organization based in São Paulo and the general population of the city, as well as between monitored and unmonitored subgroups for gamma- and X-irradiation within this worker population.

Methods: A retrospective open cohort study based on data from workers employed from 08/31/1956 to 12/31/2016, collected from the organization and official institutions. Standardized incidence ratios (SIRs) were calculated, stratified by sex, age, and calendar period, for cancer groupings by type, risk factor, organ system, and morphological aspect. Two analyses were performed: the external analysis, which compared the cancer incidence of the study population with that of the general population of São Paulo, and the internal analysis, which compared the cancer incidence of the monitored subgroup with the unmonitored subgroup for gamma and X-irradiation.

Results: The external incidence analysis showed an SIR = 0.590 (95% CI 0.537; 0.647, $p < 0.001$), and the internal incidence analysis showed an SIR = 1.066 (95% CI 0.950; 1.192, $p = 0.277$).

Conclusion: This study showed that cancer incidence was lower among all workers compared to the general population, and there was no increase in cancer incidence among those monitored for gamma and X-irradiation compared to the unmonitored subgroup. An increased incidence of thyroid cancer was observed among monitored workers and among male monitored workers.

1 | Introduction

Cancer is a multifactorial chronic disease, and occupational exposure to carcinogenic agents is a risk factor. Ionizing radiation is a carcinogen and may be present in workplace environments [1, 2]. Population studies that have evaluated the association between occupational exposure to ionizing radiation and cancer are mostly mortality studies [3], but incidence studies are becoming relevant as they can encompass preneoplastic lesions and nonfatal cancers. Preneoplastic lesions correspond to the early stages of cancer development and are of interest for study because ionizing radiation is an initiator of carcinogenesis [3]. It is estimated that the cancer incidence due to exposure to ionizing radiation at doses of 100 mSv above background radiation is 1%, but this estimate is uncertain [3]. Among survivors of the Hiroshima and Nagasaki bombings,

The study was carried out on the premises of the company, which provided the authors with access to the databases and is the employer of the first author.

there were 3155 more new cancer cases compared to deaths between 1958 and 1987, which may correspond to nonfatal cancers [4]. In a cohort study with 174,541 workers from the British nuclear industry followed from 1955 to 2001, 11,165 new cases and 7684 cancer deaths were observed in the internal analysis, showing a strong trend of increasing new cases along with rising doses [5].

During medical examinations, workers who were at risk of exposure to ionizing radiation at a company in São Paulo expressed concerns about the role of radiation in the development of cancer among them. These concerns reached the institution's senior management, who requested an investigation into this effect among workers. In response to this question and given the uncertainties surrounding cancer incidence and occupational exposure to ionizing radiation, this study aimed to compare cancer incidence between those working with ionizing radiation and the general population of São Paulo, as well as between subgroups monitored and unmonitored for gamma and X radiation exposure at a workplace unit located in São Paulo.

2 | Materials and Methods

2.1 | Study Design and Population

A historical open cohort study was conducted at a public company engaged in research, development, and applications in the radiological and nuclear fields, located in the city of São Paulo. The cohort began on 08/31/1956, the founding date of the company, and ended on 12/31/2016. The target population consisted of 6394 workers, with each worker being included in the cohort from the date they started working at the company. The follow-up ended on the date of the first cancer diagnosis or, in the absence of a cancer event, on the date of death or the cohort closure.

Inclusion criteria were having a formal employment record and at least 1 day of work at the company, from which the worker would be at risk of exposure to gamma and X radiation. Losses were considered in cases where workers refused to participate in the study or we lacked information about their vital status (alive or deceased) among those who did not have a cancer event by 12/31/2016.

2.2 | Data Sources and Collection

Identification, demographic, and employment data were obtained from the company's administrative records, and from medical and dosimetric records. The following information was collected: name, date of birth, parental information, city of origin, General Registry (RG) from the Public Security Secretary, Individual Taxpayer Registry (CPF), voter registration, employment start and end dates, initial education, job positions held, and date of death (when applicable).

Information on exposure to gamma and X radiation was obtained from monthly dosimetric records based on readings of external thoracic personal dosimeters at the company from 1961 to 2016.

Incidence data included new cancer cases and deaths, and were obtained from the company's medical and administrative records, the Population-Based Cancer Registry of São Paulo (RCBP—SP), the Mortality Information Improvement Program of the São Paulo Municipal Health Department (PRO-AIM), the Strategic Health Surveillance Information Center of the São Paulo State Health Department (CIEVS-SP), and the SEADE Foundation. The linkage technique used to consult the RCBP-SP, PRO-AIM, and CIEVS-SP databases was probabilistic (based on the matching of name, mother's name, and date of birth), while SEADE used deterministic linkage (matching name, mother's name, date of birth, father's name, city of origin, CPF, RG, employment start and end dates). For death records, preference was given to PRO-AIM death certificates, considering both the underlying and contributing causes of death.

Cancer incidence data for the city of São Paulo were obtained from the PRO-AIM database on the São Paulo city government website, covering the period from 1997 to 2015. Demographic records for the city were obtained from DATASUS [6] from the period of 1997 to 2015. The cancer records followed the International Classification of Diseases—10th Revision (ICD-10).

To determine the vital status of each worker who did not end their follow-up in the cohort due to a cancer event, a worker was considered "deceased" if death information was available, and "alive" if the worker was receiving a salary or retirement benefits. Workers were also considered alive if, through consultation with the database and the homepage of the Regional Electoral Court with national coverage [7], as well as the homepage of the Federal Revenue Service [7], they presented valid voter registration and CPF. Workers were considered "deceased" if death information was available, and "ignored" if no information could be located.

2.3 | Study Variables

Sociodemographic and employment variables collected were: sex, date of birth, employment start and end dates, date of cohort follow-up termination, age at the start and end of employment, age at the date of cohort closure, job positions, and education (categorized according to education level into high school, higher education, change from high school to higher education, and unknown).

Exposure to gamma and X radiation: workers were categorized into a monitored subgroup and an unmonitored subgroup for exposure to gamma and X radiation. The cumulative doses during employment were calculated up to the date of cohort follow-up termination [8].

Cancer categories: the cancer categories were based on the ICD-10 codes, including the group of malignant neoplasms (C00–C97) [9], preneoplastic lesions (D00–D09) [9], benign brain tumors (D32 and D33) [2], and neoplasms of uncertain behavior and hematopoietic neoplasms (D37–D48) [9]. In the external incidence analysis, cancer cases coded as C44, C78, C79, D04, D10–D44, and D48 were excluded because the PRO-AIM database did not have data on these cases for the population of São Paulo. In the internal incidence analysis, all recorded cases were included in the study.

The neoplasms were grouped according to type (solid, indeterminate, and hematopoietic), risk factors considering cancers with sufficient evidence in humans according to INCA classification and UNSCEAR (related to alcohol use, smoking, occupation, and exposure to gamma and X radiation) [10, 11], and organ systems based on the cancer classification in the ICD-10 [9] (see Figure S1A). The histological types were grouped as indeterminate (uncertain, malignant SOE, and suggestive of malignancy), carcinomas, adenocarcinomas, other neoplasms (melanomas, sarcomas, soft tissue tumors, germ cell tumors, and central nervous system [CNS] tumors), and hematological.

2.4 | Statistical Analyses

Descriptive analysis, stratified by sex, of quantitative variables was performed using means, medians, standard deviations, and minimum and maximum values. For qualitative variables, proportions were calculated. The crude incidence rates (CIR) were estimated by dividing the number of new cancer cases observed by the number of person-years, which represents the total number of years a worker was under follow-up from the entry date to the exit date of the cohort.

To compare the cancer incidence risk between the populations (exposed and unexposed), the standardized incidence ratio (SIR) was used, calculated by dividing the observed number of new cases by the expected number of new cases using the indirect method [12, 13], which is described in Supporting Material S2. The SIRs were stratified by sex, age, and calendar period. A 95% confidence interval (95% CI) was calculated to assess statistical significance.

The external analysis compared the cancer incidence of the study population with that of the city of São Paulo from 1997 to 2015. The calendar periods were 01/01/1997–12/31/2003, 01/01/2004–12/31/2009, and 01/01/2010–12/31/2015. The internal analysis compared the cancer incidence of monitored workers with that of unmonitored workers for gamma and X radiation from 1974 to 2016. The calendar periods were 01/01/1974–12/31/1995, 01/01/1996–12/31/2002, 01/01/2003–12/31/2009, and 01/01/2010–12/31/2016. The age strata at the end of the follow-up, for both the external and internal analyses, were 15.0–34.9 years, 35.0–49.9 years, and 50.0 years or older. During the study period, this general population included 162,198,362 people from the municipality of São Paulo and 556,397 new cancer cases.

2.5 | Software

For the calculation of crude and standardized rates, Microsoft Excel version 365 was used. For the descriptive analyses and calculation of 95% CI for the SIRs, STATA—Statistics/Data Analysis, version 13.1, was used.

2.6 | Ethical Aspects

The study was approved by the Research Ethics Committee of the School of Public Health at the University of São Paulo, under CAAE no. 54944616.6.0000.5421, on 08/29/2016. The company authorized the conduct of the study. Worker participation was obtained through the signing of the informed consent form. For workers who could not be contacted, the Responsibility Term was approved by the Research Ethics Committee of the São Paulo Municipal Health Department on 08/31/2018.

3 | Results

Figure 1 illustrates that, among the 6394 workers with identified records, there were 674 (10.5%) losses, with 660 due to lost follow-up and 14 due to refusal to participate, leaving 5720 (89.5%) workers. For the external analysis, an additional 130 workers were excluded, 128 due to follow-up termination before 1997 and 2 for entering the cohort in 2016, resulting in a study population of 5590 (87.4%) workers. For the internal analysis, 6 workers who ended their follow-up before 1974 were excluded, leaving 5714 (89.4%) workers.

Table 1 shows the characteristics of the study population. The majority were male (74.0%), aged 50 years or older (91.5%, mean = 61.2 years; SD = 10.0) at the end of the follow-up. The largest share (86.4%) joined the company between 1970 and 1989, held middle-level positions (66.1%), and stayed in the job for < 5 years (57.7%), with an average of

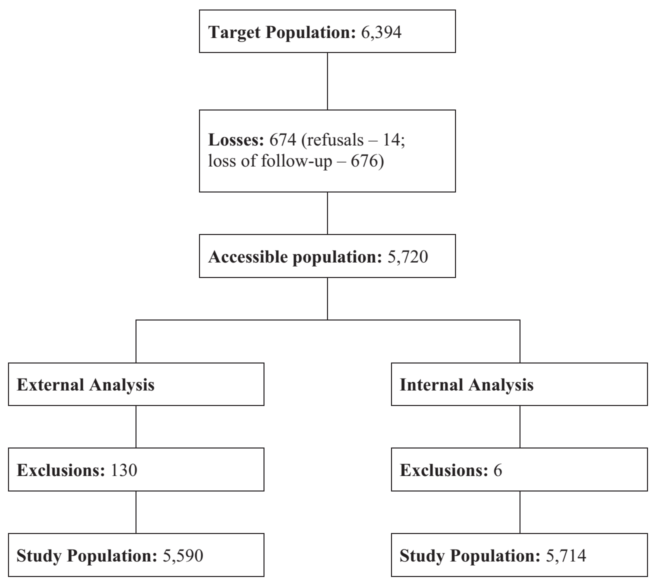

FIGURE 1 | Target population and study population, company working in research, development, and applications in the radiological and nuclear areas, São Paulo, 1993–2016.

TABLE 1 | Characteristics of the study population according to gender, company working in research, development, and applications in the radiological and nuclear areas, São Paulo, 1956–2016.

Variable	Men		Women		Total	
	N	%	*N*	%	*N*	%
Age range at the end of follow-up (years)						
15–35	60	1.4	16	1.1	76	1.3
35–50	271	6.4	137	9.2	408	7.1
≥ 50	3900	92.2	1330	89.7	5230	91.5
Calendar period for entry into employment						
1956–1959	49	1.2	9	0.6	58	1.0
1960–1969	280	6.6	108	7.3	388	6.8
1970–1979	1835	43.4	733	49.4	2568	44.9
1980–1989	1877	44.4	493	33.2	2370	41.5
1990–1999	100	2.4	84	5.7	184	3.2
2000–2016	90	2.1	56	3.8	146	2.6
Employment time (years)						
< 1.0	936	22.1	257	17.3	1193	20.9
1.0–4.9	1643	38.8	462	31.2	2105	36.8
5.0–9.9	461	10.9	186	12.5	647	11.3
10.0–19.9	352	8.3	165	11.1	517	9.0
20.0–29.9	295	7.0	204	13.8	499	8.7
30.0–39.9	473	11.2	177	11.9	650	11.4
40.0–49.9	69	1.6	32	2.2	101	1.8
50.0 or more	2	0.0	0	0.0	2	0.0
Characteristics of the position held						
Mid-level position	2904	68.6	875	59.0	3779	66.1
Higher-level position	1004	23.7	432	29.1	1436	25.1
Mixed positions (middle and higher)	257	6.1	108	7.3	365	6.4
Unknown	66	1.6	68	4.6	134	2.3
Risk of exposure to gamma and X radiation						
No	1688	39.9	702	47.3	2390	41.8
Yes	2543	60.1	781	52.7	3324	58.2
Total	4231	100.0	1483	100.0	5714	100.0

9.5 years (SD = 12.3). The average follow-up time in the cohort was 34.9 years (SD = 9.2).

External monitoring for gamma and X radiation was identified in 58.2% of the workers, and among them, 69.5% had a cumulative dose below 10.0 mSv. The mean cumulative dose was 14.8 mSv (SD = 35.7), with a median of 3.0 mSv, a minimum of 0.0 mSv, and a maximum of 656.2 mSv.

At the end of the follow-up, 528 (9.2%) new cancer cases were reported. Table 2 presents the distribution of the new cancer cases. The most common type was solid cancer (88.1%). For cancer risk factors, 68.4% were identified with cancers related to work, 59.3% with those related to exposure to gamma and X radiation, 39.0% with exposure to smoking, and 31.1% with alcohol use. The proportion of cancers related to alcohol use and smoking was higher among men, while those related to work and gamma and X radiation exposure were more common among women.

By organ system, the highest proportion of cancer was observed in the genitourinary system (32.8%), with 28.1% among men and 42.6% among women. Digestive system cancers (22.9%) were more frequent among men (25.1%) than women (18.3%). Skin cancers (12.3%), respiratory system cancers (10.8%), and hematopoietic cancers (7.0%) were also notable.

By cancer site, the most frequent neoplasms were prostate cancer with 69 cases (19.2% among men) and breast cancer with

TABLE 2 | Distribution of new cancer cases and gender, company working in research, development, and applications in the radiological and nuclear areas, São Paulo, 1974–2016.

Variable	Men		Women		Total	
	N	%	*N*	%	*N*	%
Type						
Solid	313	87.2	152	89.9	465	88.1
Indeterminate	18	5.0	8	4.7	26	4.9
Hematogenous	28	7.8	9	5.3	37	7.0
Risk factor[a]						
Related to alcoholism	81	22.6	83	49.1	164	31.1
Related to smoking	154	42.9	52	30.8	206	39.0
Work-related	224	62.4	137	81.1	361	68.4
Gamma and X radiation	187	52.1	126	74.6	313	59.3
Morphology						
Malignant neoplasm not otherwise specified (SOE)	117	32.6	49	29.0	166	31.4
Carcinoma	84	23.4	36	21.3	120	22.7
Adenocarcinoma	112	31.2	75	44.4	187	35.4
Other solid neoplasms	22	6.1	3	1.8	25	4.7
Hematological neoplasms	24	6.7	6	3.6	30	5.7
Organic system						
Digestive	90	25.1	31	18.3	121	22.9
Respiratory	44	12.3	13	7.7	57	10.8
Genitourinary	101	28.1	72	42.6	173	32.8
Musculoskeletal	6	1.7	2	1.2	8	1.5
Skin	50	13.9	15	8.9	65	12.3
Eyes and central nervous system	9	2.5	3	1.8	12	2.3
Endocrine	13	3.6	15	8.9	28	5.3
Hematopoietic	28	7.8	9	5.3	37	7.0
Indeterminate	18	5.0	9	5.3	27	5.1
Main position held						
Mid-level position	213	59.3	101	59.8	314	59.5
Higher-level position	117	32.6	53	31.4	170	32.2
Mixed position (middle and high)	26	7.2	13	7.7	39	7.4
Unknown	3	0.8	2	1.2	5	0.9
Total	359	100.0	169	100.0	528	100.0

[a]The sum of the categories does not correspond to 100.0% because the worker may have been exposed to more than one risk factor.

53 cases (31.4% among women). Nonmelanoma skin cancer (NMSC) had 53 cases (10.0%), colorectal neoplasms had 49 cases (9.3%), and neoplasms of the bronchi and lungs had 41 cases (7.8%). Details about the number of new cases by ICD-10 codes are presented in Table S1A.

By morphology, the highest frequencies of new cases were adenocarcinomas (35.4%) and neoplasms not otherwise specified (31.4%).

Evalauting cancers by positions held, the highest proportion of new cancer cases was found in the middle-level positions category (59.5%), followed by the higher-level positions category (32.2%).

The cancer CIR of the whole cohort study was 467.8 new cases/100,000 person-years; for males, it was 434.2/100,000 person-years, and for females, it was 563.0/100,000 person-years.

Among the 5590 participants in the external analysis, 459 (8.2%) new cancer cases occurred. Table 3 shows the SIRs in the external analysis. A lower risk of all new cancer cases in the study population was observed, with an SIR of 0.590

TABLE 3 | Cancer incidence—external comparison[a]: number of observed and expected new cases, standardized incidence ratio and 95.0% confidence interval, according to sex and new case of cancer, company working in research, development, and applications in the radiological and nuclear areas, São Paulo, 1997–2015.

	Men				Women				Total			
Cancer groups	**O**	**E**	**SIR**	**CI**	**O**	**E**	**SIR**	**CI**	**O**	**E**	**SIR**	**CI**
All cancers	315	607.4	0.519	0.463; 0.579	144	170.4	0.845	0.713; 0.995	459	777.8	0.590	0.537; 0.647
Type												
Solid	276	540.5	0.511	0.452; 0.575	129	151.5	0.851	0.711; 1.012	405	692.0	0.585	0.530; 0.645
Indeterminate	14	32.4	0.432	0.236; 0.725	6	9.6	0.624	0.228; 1.359	20	42.0	0.476	0.291; 0.735
Hematogenous	25	34.5	0.724	0.469; 1.069	9	9.3	0.969	0.442; 1.839	34	43.8	0.776	0.538; 1.085
Risk factor												
Related to alcoholism	72	199.9	0.360	0.282; 0.454	72	85.3	0.844	0.660; 1.063	144	285.2	0.505	0.426; 0.595
Related to smoking	137	310.8	0.441	0.370; 0.521	44	64.5	0.683	0.496; 0.917	181	375.2	0.482	0.415; 0.558
Work-related	197	309.8	0.636	0.550; 0.731	117	125.7	0.931	0.770; 1.115	314	435.5	0.721	0.643; 0.805
Gamma and X radiation	162	263.2	0.615	0.524; 0.718	106	113.1	0.937	0.767; 1.133	268	376.4	0.712	0.629; 0.803
Organic system												
Digestive	79	194.5	0.406	0.322; 0.506	29	39.9	0.727	0.487; 1.044	108	234.4	0.461	0.378; 0.556
Respiratory	41	79.4	0.516	0.371; 0.701	10	10.2	0.981	0.470; 1.805	51	89.6	0.569	0.424; 0.749
Genitourinary	89	239.7	0.371	0.298; 0.457	60	86.9	0.691	0.527; 0.889	149	326.5	0.456	0.386; 0.536
Musculoskeletal	6	6.2	0.973	0.355; 2.117	2	1.8	1.128	0.127; 4.080	8	7.9	1.007	0.434; 1.985
Skin	5	0.2	20.4-76	6.714; 48.617	1	0.1	16.574	0.218; 92.719	6	0.3	19.7-03	7.303; 43.533
Eyes and central nervous system	6	9.0	0.670	0.245; 1.458	3	4.3	0.690	0.139; 2.015	9	13.3	0.676	0.309; 1.285
Endocrine	9	9.8	0.923	0.421; 1.752	13	10.1	1.288	0.685; 2.203	22	19.8	1.109	0.695; 1.679
Hematopoietic	25	34.8	0.719	0.465; 1.061	9	12.2	0.740	0.337; 1.404	34	47.0	0.724	0.501; 1.012
Indeterminate	14	33.8	0.414	0.226; 0.694	7	9.8	0.715	0.286; 1.473	21	43.6	0.481	0.298; 0.736
Morphology												
Malignant neoplasm SOE	97	91.7	1.058	0.858; 1.291	36	27.5	1.309	0.916; 1.812	133	119.2	1.116	0.934; 1.323
Carcinoma	79	189.3	0.417	0.330; 0.520	26	35.0	0.743	0.485; 1.089	105	224.3	0.468	0.383; 0.567
Adenocarcinoma	100	321.0	0.312	0.253; 0.379	70	94.4	0.742	0.578; 0.937	170	415.4	0.409	0.350; 0.476
Other solid neoplasms	14	13.3	1.050	0.574; 1.762	3	4.2	0.710	0.143; 2.077	17	17.6	0.968	0.564; 1.550
Hematology	25	34.8	0.718	0.465; 1.061	9	9.3	0.963	0.440; 1.829	34	44.1	0.770	0.533; 1.076

Abbreviations: CI, confidence interval 95.0%; E, new cases expected; O, new cases observed; SIR, standardized incidence ratio.
[a]Standardization by sex, age group, and calendar period, using the indirect standardization method, taking as the standard population the population of the Municipality of São Paulo in the respective calendar period.

(95% CI 0.537; 0.647) when compared to the population of São Paulo, as well as in the male and female strata.

Similar results were observed for new solid and indeterminate cancer cases between all workers and men, but no significant differences were found among women or for hematological cancers among men.

In examining risk factors, a significantly lower risk was observed in the total study population and in the male stratum for alcohol use, smoking, work, and gamma and X radiation exposure. Among women, a lower risk was observed only for smoking.

Differences in organ system cancers by sex were also seen. A lower risk was found in the study population and among men for cancers of the digestive, respiratory, genitourinary, and indeterminate systems. Among women, the lower risk occurred only for the genitourinary system. An exception was found for skin cancers, where there was a higher risk among the total workers (SIR = 19.703; 95% CI 7.303; 43.533) and among men (SIR = 20.476; 95% CI 6.714; 48.617).

The total study population and the male stratum showed a lower risk for carcinoma and adenocarcinoma when compared to the population of São Paulo.

Table 4 shows the SIR in the internal analysis. An increased risk of new cancers across all types was observed in the monitored subgroup with an SIR of 1.066 (95% CI 0.950; 1.192). There were no statistically significant differences in new cancer cases between the monitored and nonmonitored subgroups in the male and female strata.

Hematological cancers showed a statistically significant increase in the risk of new cases in the monitored subgroup, but without differences in the male and female strata. Indeterminate cancers showed a statistically significant increase in the risk of new cases among the monitored women.

By organ system, skin cancers showed an increased risk in the monitored subgroup as well as in both male and female strata. In the monitored subgroup, an increased risk was also observed for cancers of the hematopoietic, musculoskeletal, and endocrine systems, while in the male stratum, an increased risk was noted for musculoskeletal and endocrine cancers. Among women, an increased risk was observed for cancers of unspecified sites. The similarity of the results observed between the monitored subgroup and the male stratum highlights the predominance of this gender within the study population. Respiratory system cancer cases showed a statistically significant lower risk of new cases in the monitored subgroup as a whole and among monitored men.

There was a statistically significant increase in the risk of new carcinomas, other solid neoplasms, and hematological cancers in the monitored subgroup compared to the nonmonitored subgroup. Among men, a statistically significant increase was found in other solid neoplasms, and among women, there was a statistically significant increase in carcinomas.

It is noteworthy that, for some cancer groups, particularly among women, there were a small number of cases, which did not provide statistical stability for the results.

4 | Discussion

This study aimed to compare the cancer incidence among workers in the radiological and nuclear areas of a company located in São Paulo with the general population of the same municipality, as well as between monitored and nonmonitored workers for gamma and X-ray radiation.

The highest absolute number of new cancer cases was observed in males, but females showed the highest proportion. Women presented a higher cancer incidence density compared to men.

These results are consistent with incidence studies that reported data on nonfatal cancers with higher survival rates, such as breast and thyroid cancers, which are more common in women [4]. In the study of atomic bomb survivors, females accounted for 56% of new cancer cases, while males accounted for 44% [4, 14, 15]. This highlights the differences between incidence and mortality in both sexes. Cancer incidence is higher among women due to their greater likelihood of being affected by nonfatal cancers, while men tend to be affected by more aggressive cancers with higher mortality rates, such as stomach cancer [16]. In this study, the proportion of digestive tract cancers was higher among men.

Prostate cancer, breast cancer, NMSC, and colorectal cancer were the most incident types in the study population. The frequency of these cancers in the study population differs from that observed in the general population of São Paulo, where NMSC is the most common [17, 18]. These findings suggest underreporting of NMSC cases in the study population, as this group of neoplasms is often underreported, even in the official cancer registries of São Paulo.

4.1 | External Analysis

The SIRs in the external analysis showed that the risk of new cancer cases, excluding NMSC, in the study population was lower when compared to the population of São Paulo. These results suggest the healthy worker effect is operating [19].

The healthy worker effect was extended to the analysis of the incidence of all combined cancers and has been observed in other studies conducted in companies in the United Kingdom [20–22], France [23], the United States [24], and Canada [19]. The SIR for all cancers was higher for women than for men, indicating that women had a higher cancer incidence than men. However, both sexes showed a lower risk of new cancer cases compared to the populations of São Paulo.

The higher cancer incidence in women raises the possibility of an association with occupational exposure to ionizing radiation, as women are more sensitive to ionizing radiation [15, 25], and thyroid and breast tissues are more sensitive to ionizing radiation

TABLE 4 | New cancer cases—internal comparison[a]: number of observed and expected deaths, standardized mortality ratio, and 95.0% confidence interval, according to sex and cause of death, company working in research, development, and applications in radiological and nuclear areas, São Paulo, 1974–2016.

	Men				Women				Total			
Cancer groups	**O**	**E**	**SIR**	**CI**	**O**	**E**	**SIR**	**CI**	**O**	**E**	**SIR**	**CI**
All cancers	217	203.9	1.064	0.927; 1.216	90	84.2	1.069	0.860; 1.314	307	288.1	1.066	0.950; 1.192
Type												
Solid	187	182.1	1.027	0.885; 1.185	78	79.1	0.986	0.780; 1.231	265	261.1	1.015	0.896; 1.145
Indeterminate	11	9.2	1.198	0.597; 2.144	6	2.0	2.943	1.074; 6.402	17	11.2	1.515	0.882; 2.426
Hematogenous	19	12.6	1.503	0.905; 2.347	6	3.1	1.961	0.716; 4.268	25	15.7	1.593	1.030; 2.351
Risk factor												
Related to alcoholism	41	59.1	0.694	0.498; 0.942	39	46.5	0.838	0.596; 1.146	80	105.6	0.757	0.601; 0.943
Related to smoking	81	104.9	0.772	0.613; 0.960	23	30.2	0.762	0.483; 1.143	104	135.1	0.770	0.629; 0.933
Work-related	138	126.1	1.094	0.919; 1.293	72	62.1	1.160	0.907; 1.460	210	188.2	1.116	0.970; 1.277
Gamma and X radiation	115	104.6	1.099	0.907; 1.319	74	66.7	1.109	0.871; 1.392	189	171.3	1.103	0.951; 1.272
Organic system												
Digestive	47	61.5	0.764	0.558; 1.010	15	16.8	0.893	0.500; 1.474	62	78.3	0.792	0.607; 1.015
Respiratory	18	37.0	0.486	0.288; 0.769	6	7.3	0.817	0.298; 1.779	24	44.4	0.541	0.347; 0.805
Genitourinary	62	56.1	1.104	0.847; 1.416	32	42.0	0.762	0.521; 1.076	94	98.1	0.958	0.774; 1.172
Musculoskeletal	5	1.5	3.256	1.046; 7.577	2	0.0	—	— —	7	1.5	4.559	1.821; 9.366
Skin	36	21.5	1.672	1.170; 2.314	13	2.0	6.377	3.390; 10.898	49	23.6	2.078	1.538; 2.748
Eyes and central nervous system	7	3.1	2.279	0.913; 4.698	0	3.3	0.000	— 1.222	7	6.3	1.105	0.442; 2.275
Endocrine	12	1.3	9.356	4.839; 16.377	9	7.7	1.174	0.535; 2.228	21	9.0	2.346	1.452; 3.587
Hematopoietic	19	12.6	1.503	0.905; 2,347	6	3,1	1.961	0.716; 4.268	25	15.7	1.593	1.030; 2.351
Indeterminate	11	9.2	1.198	0.597; 2.144	7	2.0	3.434	1.375; 7.070	18	11.2	1.604	0.950; 2.536
Morphology												
Malignant neoplasm SOE	63	70.4	0.895	0.687; 1.45	18	28.9	0.622	0.368; 0.983	81	99.4	0.815	0.647; 1.013
Carcinoma	54	44.5	1.213	0.912; 1.583	25	11.3	2.210	1.430; 3.263	79	55.8	1.415	1.120; 1.764
Adenocarcinoma	64	69.6	0.919	0.708; 1.173	40	38.7	1.034	0.739; 1.408	104	108.3	0.960	0.784; 1.163
Other solid neoplasms	17	6.7	2.548	1.484; 4.081	1	2.2	0.459	0.006; 2.552	18	8.8	2.034	1.205; 3.215
Hematology	19	12.6	1.503	0.905; 2.347	6	3.1	1.961	0.716; 4.268	25	15.7	1.593	1.030; 2.351

Abbreviations: CI, confidence interval 95.0%; E, new cases expected; O, new cases observed; SIR, standardized incidence ratio.
[a]Standardization by sex, age group, and calendar period, using the indirect standardization method, taking as the standard population the study population not monitored to gamma and X radiation in the respective calendar period.

than bone marrow [26]. However, the SIR indicated that there was no statistically significant difference in the incidence of radiogenic cancers between women in the study population and women in the general population. The radiogenic cancer category included cancers with sufficient evidence in humans [10] and represented exposure to gamma and X radiation. Further studies are needed to elucidate the contribution of other factors that may be involved in this outcome.

Regarding socioeconomic status, new cancer cases showed a higher proportion among mid-level job positions in the study population. This indicates that cancer is more frequent in lower social strata [27] but also highlights the study population's access to healthcare, including the company's medical insurance and the occupational health service available to all employees, which allows for the screening of prostate, breast, and other cancers.

Solid cancers accounted for 88.1% of new cancer cases. This result may be a consequence of the availability of data on new cancer cases, which has been available in São Paulo only since 1997, corresponding to a later period of cohort follow-up. This could have facilitated the identification of a larger number of records for solid cancers compared to hematogenic cancers, considering that solid cancers manifest later and hematogenic cancers manifest earlier after exposure to ionizing radiation [28–31].

Solid, hematogenic, and indeterminate cancers showed a lower risk of incidence in the study population, as well as in both male and female strata. Studies on hematogenic cancers, which include the more aggressive cancers associated with ionizing radiation exposure, are more commonly addressed in mortality studies. Few studies on the incidence of hematogenic cancers have been conducted, but research on British company workers that compared the incidence of solid and hematogenic cancers showed a similar result, that is, no statistically significant association was found. Solid cancers had a similar incidence to that of the general English population, while hematogenic cancers showed a significantly lower incidence [32].

Risk factors were evaluated by grouping cancers with sufficient evidence in humans [33]. Alcohol consumption and smoking showed the lowest statistically significant results among the risk factors investigated, indicating that they were not significant cancer risk factors here. An exception was observed for alcohol consumption in women, which showed no statistically significant difference compared to the female population of São Paulo, possibly due to breast cancer, which is associated with alcohol consumption and was the most common cancer among women. As in this study, other studies in the literature have shown that nuclear sector workers tend to lead healthier lifestyles than the general population [32, 34].

Most carcinogenic agents present in workplaces are chemical substances, but this study did not have access to records on occupational exposure to chemicals. This grouping allowed an indirect assessment of the contribution of chemical exposure and showed a statistically significant decrease in the risk of new cancer cases in the study population and among men. Among women, the risk of new cases was not different from that of the female population of São Paulo.

As for gamma and X radiation, there was a statistically significant lower risk of new cancer cases in the study population and among men. Among women, there was no difference compared to the female population of São Paulo, indicating that it is unlikely that ionizing radiation in the workplace is associated with new cancer cases.

Among organ systems, the only one that showed a statistically significant association in the study population, for both men and women, was the skin. In this study, the only types of skin cancer present were melanoma and melanoma in situ. Melanoma is a rare cancer with few cases recorded in the study population and in São Paulo, which did not provide statistical stability to the results. However, this result does not rule out the possibility that individual cases may be related to occupational exposure.

4.2 | Internal Analysis

The SIR for all new cases showed no statistically significant difference in the incidence of new cancer cases between the two subgroups, as well as in the male and female strata. Similar results have been observed in the literature [20, 32, 35, 36].

By types of cancer, a statistically significant increase in hematogenous cancers was observed, also reflected in the hematopoietic organ system and the hematological morphological category within the monitored subgroup. However, no statistically significant differences were noted between the male and female strata. Due to the low number of leukemia, lymphoma, and other hematological malignancy cases, an individualized analysis of these cancers within this study would not rule out a spurious result. In the literature, individualized studies on the incidence of leukemias [20, 22, 32, 36], lymphomas, and multiple myeloma [37] have shown variable results.

Given that leukemias are clearly associated with exposure to ionizing radiation [3], analyzing the radiogenic cancer category in this study might offer some indirect information. The results, however, also did not indicate an association. Nonetheless, further studies are needed to clarify the observed association between hematological cancers and occupational exposure to ionizing radiation.

In the internal analysis, the monitored female subgroup showed a statistically significant increase in the incidence of indeterminate cancers compared to the nonmonitored subgroup. Indeterminate cancers are those identified through metastases, where the primary site remains unknown even after detailed investigation [38]. Clinically, these are aggressive diseases that spread rapidly [39]. This result is difficult to interpret but may be a chance finding due to the small number of cases observed among monitored women.

Alcohol consumption and smoking did not emerge as risk factors for cancer among monitored workers, as observed in studies in the literature [21, 22, 32, 34, 40]. This suggests that monitored workers may have a healthier lifestyle than nonmonitored workers. Concerning workplace risk factors and ionizing radiation, no statistically significant increase in risk was found in the monitored subgroup or in the male and female strata.

With respect to organ systems, associations were found with skin cancers, musculoskeletal system cancers, and endocrine system cancers.

Among skin cancers, both melanoma and NMSC were included, which allowed for a larger number of skin cancer cases. Despite the statistically significant increase in risk, NMSC reporting often contains gaps, and the review of company medical records suggests better documentation among monitored workers. This is relevant since skin carcinomas, especially basal cell carcinomas, are associated with exposure to ionizing radiation [11]. Although a positive association was observed for NMSC in the monitored subgroup and in the male stratum, it cannot be ruled out that solar exposure may also play a role in these skin cancers, as NMSC is strongly associated with exposure to ultraviolet radiation [11].

For cancers of the musculoskeletal system, there was a statistically significant increase in risk among men and in the monitored subgroup as a whole. Bone cancer is a rare type of cancer, and only a few cases were found in this study, which does not rule out the possibility of the result being due to chance.

Endocrine system cancers are predominately thyroid cancers. The association between ionizing radiation exposure and thyroid cancer is well-documented [41], and the thyroid is the most radiation-sensitive tissue [26]. Since thyroid cancer typically has a good prognosis, it appears more frequently in incidence studies. The increased risk observed among monitored men and in the monitored subgroup as a whole reflects the majority participation of men in the study population and may also suggest a possible increase in case reporting among monitored workers. As thyroid cancer is a traceable type of cancer, any positive result should be interpreted with caution [5].

Thyroid cancer is more common in women, but in this study, it was more frequent among men, highlighting the need for further research to clarify the observed result. Some studies conducted in British companies have reported thyroid cancer results in mortality studies, but these were not statistically significant [36, 42, 43].

By morphology, a statistically significant association was found for carcinomas and other solid neoplasms, in addition to the hematopoietic cancers already observed. The association for carcinomas was likely influenced by NMSC and breast cancers among women. The “other solid neoplasms” category showed a statistically significant association due to musculoskeletal cancers and CNS neoplasms, with the latter showing a marginal association in men. This morphological category was statistically significant in men. The incidence of CNS neoplasms showed a statistically significant increase among men in a study conducted at a US company [24], but other studies have not confirmed this association.

5 | Strengths and Limitations

The primary limitation of the study was related to the accessibility and quality of the data. In the external analysis, the lack of access to records of new cancer cases prior to 1997 and in other locations was a significant constraint. Records of new cases were limited to those available at the company and in the municipality of São Paulo. However, one benefit was the inclusion of mortality records from the state of São Paulo, which helped minimize gaps in cancer case reporting. This is particularly relevant since São Paulo has the highest socioeconomic level in Brazil and the best mortality records.

Another strength of this study was the 60-year follow-up of a worker cohort, a desirable period for analyzing cancer incidence. Additionally, it allowed for the analysis of a population with the majority of participants aged over 50 years—both men and women—which is an ideal age range for cancer incidence analysis.

The stratified analysis by sex was a positive aspect of this study, as such differentiation is uncommon in research on workers in the nuclear industry. Both the external and internal analyses allowed for the observation of differences in cancer incidence between men and women in the study population compared to the general population, as well as between monitored and nonmonitored subgroups for gamma and X-ray radiation exposure. This differentiation was fundamental for understanding gender aspects and the profile of new cancer cases.

The internal analysis of cancer incidence, despite the limitations related to the registration of new cases, was a success as it included the entirety of new cases and nearly the entire study population. Another achievement was the inclusion of NMSC cases due to the identification of records in the company's medical files, enabling the analysis of skin cancer incidence. Similarly, the analysis of lesions with uncertain behavior and in situ lesions strengthened the research, as it expanded the study of the carcinogenic effects of ionizing radiation. This is important because ionizing radiation is a carcinogenic agent that acts in the first phase of carcinogenesis by causing mutations in DNA molecules [3].

Additionally, comparing the monitored subgroup to the nonmonitored subgroup provided the advantage of analyzing closely related populations, minimizing biases related to the healthy worker effect [12]. The internal analysis based on dose strata was not appropriate in this study since 70% of the study population had a cumulative dose of < 10 mSv, with few cases at higher exposures, which compromises the statistical stability of the analyses.

Since the number of new cancer cases exceeds the number of deaths due to the inclusion of nonfatal cancers, such as thyroid and breast cancers, the SIR analysis, even when dividing the study population into two subgroups, provided informative results about the association between cancer and occupational exposure to gamma and X-ray radiation.

Although international cohorts of nuclear industry workers have been conducted in developed countries with a larger number of participants [5, 19–24, 27, 32, 34–36, 41–43], this cohort had a significant number of workers for a company of considerable importance in the nuclear sector of a developing country. This contributed to national knowledge and the scientific literature.

6 | Practical Implications

This study revealed a lower cancer incidence compared to the population of São Paulo, corresponding to the healthy worker effect and highlighting the benefits of workplace protective measures, as well as disease prevention and health promotion initiatives provided by occupational health services and access to healthcare.

The internal analysis showed a positive association for skin and thyroid cancers among men and in the overall study population. However, this result may be influenced by reporting limitations. Despite this, the study provides valuable insights for the routine and systematic practices of occupational health and safety professionals. It emphasizes the importance of understanding cancer incidence, including nonfatal cancers and preneoplastic lesions, which are detected through early diagnosis. Early detection leads to appropriate treatment and reduces fatal outcomes. This can be attributed to the quality of protective measures in the workplace and the health monitoring of these workers.

In conclusion, this study demonstrated a lower risk of cancer incidence in the study population and in the subgroup monitored for gamma and X-ray radiation for various types of cancers, such as those of the genitourinary and digestive tracts. On the other hand, an increased risk was observed for skin and thyroid cancers among monitored workers. These findings point to the healthy worker effect and underscore the importance of protective measures in the workplace, as well as occupational health and disease prevention efforts in safeguarding worker health.

Author Contributions

Conception, work supervision, planning, analysis, and interpretation were carried out by Glacy Sabra Vieira and Maria Carmen Martinez. The final writing was done by Glacy Sabra Vieira. All authors approve the final version submitted.

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Ethics Statement

The study was approved by the Research Ethics Committee of the School of Public Health at the University of São Paulo, under CAAE no. 54944616.6.0000.5421.

Consent

Worker participation was obtained through the signing of the informed consent form.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.