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The magnitude of the association between smoking and the risk of developing cancer in Brazil: a multicenter study

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ABSTRACT

Objectives: To estimate the magnitude of association and identify the aetiological fraction (AF) attributable to smoking in the development of different types of cancers in Brazil.

Setting: We conducted a case–control study, including 231 102 patients registered in the Cancer Hospital Registries (CHR) in the period from 1998 to 2011.

Participants: A total of 204 131 cancer cases relating to 30 topographies were compared with 26 971 cases of non-melanoma skin cancer.

Primary and secondary outcome measures: Smoking exposure was considered at the time of hospital registration. We calculated OR, unadjusted and adjusted for gender, age and alcohol consumption, with 95% CIs.

Results: After adjustment, the risk of developing cancer associated with smoking was very high (piriform sinus, bronchi and lung, larynx, hypopharynx, oropharynx and oral cavity), high (oesophagus and bladder), moderate (anus and anal canal stomach, nasal cavity, middle ear and paranasal sinuses, pancreas, nasopharynx, other parts of the biliary tract and kidney and low (liver, gall)). There was no association between smoking and cancers of the central nervous system and myeloid leukaemia. For thyroid cancer there was a decreased risk of developing the disease. The AF was higher than 50% for hypopharynx, larynx, bronchi and lung, oropharynx, oral cavity and oesophagus cancers.

Conclusions: This study confirms a high risk of developing cancer of the hypopharynx, bronchi and lung, larynx, oropharynx and oral cavity, oesophagus and bladder cancer among smokers and establishes the AF attributable to smoking in the development of different types of cancer in Brazil.

Strengths and limitations of this study

- The limitation of this study is that it is based on the analysis of secondary data, with data collected in a large number of cancer treatment centres, making it difficult to standardise data collection. A strong point is that the association between smoking and cancer was adjusted for alcohol consumption. Even with these limitations, the opportunity to define the magnitude of the risk of developing cancer associated with tobacco use and the fraction of cancers that can be attributed to its consumption by a large Brazilian national study allowed, for the first time in the country, to give a comprehensive overview of this association.

INTRODUCTION

According to the WHO, cancer is the leading cause of death worldwide, with approximately 27 million incident cases, 17 million deaths and 75 million people living with the disease being estimated for the year 2030.[1]

Smoking is the main risk factor for the development of many types of cancer. According to the International Agency for Research on Cancer (IARC), tobacco smoking is associated with cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, oesophagus, stomach, colon and rectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, uterine cervix, ovary (mucinous), urinary bladder, kidney (body and pelvis), ureter and bone marrow (myeloid leukaemia).[2] These tobacco-related cancers account for almost half of the global neoplastic disease burden. The WHO[3] estimates that, each year, six million people die as a result of tobacco use and if this situation is not reversed in 2020, there will be about 7.5 million deaths annually.

In Brazil, according to data released by the Brazilian National Cancer Institute (NCI), tobacco use kills about 200 000 people/year.[4] Measures adopted in the country for tobacco control, contributed to the decline of 50% in

the median prevalence of tobacco use in the past two decades.[4–6] Brazil has a mixed population composition with varied genetic, epidemiological and sociodemographical characteristics, which may result in differential association between smoking and different types of cancer, and the empirical evidence of this association is relatively scarce in the country. Consequently, well-designed epidemiological studies are necessary to assess the risk of disease and the fraction of cancers that can be attributed to tobacco use. Therefore, this study aims to estimate the magnitude of the association between smoking and the development of different types of cancers and to identify the aetiological fraction (AF) attributable to tobacco.

MATERIALS AND METHODS

An observational study was conducted using secondary data from Cancer Hospital Registries (CHR), provided by the Brazilian NCI through the *Integrator CHR System*, which gathers information on hospitalisations for cancer in Brazil. The data were taken in September 2011 and refer to cases for which the hospital provided the initial diagnosis of cancer and/or for which the hospital contributed to first course treatment (analytic cases), diagnosed between 1998 and 2011 and seen in 168 reference centres for cancer treatment, accredited by the Brazilian Government, in 24 Brazilian states.

We adopted a case–control study design. Cancer cases from 32 sites were compared with cases of non-melanoma skin cancer, as they are not related to tobacco use and information was available in the database. We excluded patients younger than 18 years and older than 100 years, those with no information on gender and smoking, the main purpose of this research. Cancers with fewer than 50 cases with valid data were excluded, in order to render the analysis more precise.

The data set collected in each case includes variables such as demographics, tumour characteristics (cancer type, extent, location, etc), initial treatments and history of current alcohol consumption (more than three times per week, independent of amount consumed). The exposure variable was the report of habitual tobacco use and its derivatives at the time of hospital enrolment, categorised as yes or no.

Statistical analysis was performed using the PASW Statistics software, V.18. We conducted a descriptive analysis of the population. Percentages were calculated based on valid data (ie, missing data were excluded). Association between tobacco use and cancer occurrence was analysed using OR with 95% CIs. In order to control for confounding factors or interactions, an adjusted analysis was performed considering age, gender and alcohol consumption, factors associated with both exposure and outcome. Variables completely outside the system of interest and variables only associated with the exposure or outcome were not included in the final model in order to avoid unnecessary regression adjustment and improve precision of estimators. The adjusted ORs were classified as: no association (OR<1); small effect or weak association (OR 1–1.5), medium or moderate association (OR 1.5–2.5); large or strong association (OR 2.5–4) and very large or very strong association (OR>4). For cancers associated with tobacco use, we calculated the AF or the population attributable risk fraction, in order to estimate the proportion of cancer cases that could be avoided if the population had not been exposed to tobacco. The AF was calculated using the formula: $AF=Pc(aOR-1)/aOR$, where aOR denotes the adjusted OR and Pc is the proportion of cases exposed.[7] Once relative risk (RR) was replaced by OR the computing formula will approximate the excess fraction only insofar as the OR approximates the RR.

RESULTS

A total of 204 131 cancer cases were compared with 26 971 controls. In men, there was a predominance of prostate cancer, followed by bronchi and lung and oral cavity; in women, breast cancer, uterine cervix, and colon and rectum were more prevalent (table 1).

Regarding social and demographic variables, a high prevalence of patients aged 50 years or more (71.4%), race/skin colour white (59.0%), with eight or fewer years of schooling (81.1%) and living with a partner (60.1%) was observed. In addition, 29.2% had a history of alcohol and 47.9% reported tobacco consumption (table 2).

The risk of cancer associated with smoking, adjusted for gender, age and alcohol consumption, was very strong for cancers of the hypopharynx, bronchi and lung, larynx, oropharynx and oral cavity. Tobacco was classified as a strong risk factor for cancers of the oesophagus and bladder. A moderate risk was observed for cancers of the anus and anal canal, stomach, nasal cavity, middle ear and sinuses, pancreas, nasopharynx, other parts of the biliary tract and kidney. There was a weak association with liver cancer, gallbladder, and colon and rectum. There was no association between smoking and cancers of the central nervous system and myeloid leukaemia. For thyroid cancer, the effect of smoking was associated with a 20% reduction in the risk of developing the disease (table 3).

The AF results referring to cancer sites for both genders was above 50% for cancers of the piriform sinus, larynx, hypopharynx, bronchi and lung, oropharynx, oral cavity, and oesophagus. Intermediate fractions (10–50%) were observed for cancers of the bladder, stomach, nasal cavity, middle ear and paranasal sinuses, anus and anal canal, nasopharynx, pancreas, other parts of biliary tract, kidney and liver. Fractions less than 10% were observed in cancers of the colon and rectum and bladder (table 3).

For women, intermediate aetiological fractions were observed for cervix (20.1%), ovary (19.9%) and vulva

Table 1 Cancer sites according to gender (n=231 102)

Cancer site	ICD-O-3	Male	Female	Total
Oral cavity	C00–C08	9080	3108	12 188
Oropharynx	C10	2458	435	2893
Nasopharynx	C11	740	312	1052
Piriform sinus	C12	651	59	710
Hypopharynx	C13	1429	168	1597
Oesophagus	C15	6884	2043	8927
Stomach	C16	6861	3508	10 369
Colon and rectum	C18–C20	7813	7976	15 789
Anus and anal canal	C21	375	1123	1498
Liver	C22	750	411	1161
Gallbladder	C23	129	432	561
Other parts of the biliary tract	C24	199	191	390
Pancreas	C25	918	804	1722
Nasal cavity, middle ear and sinuses	C30–C31	525	321	846
Larynx	C32	6574	993	7567
Bronchi and lung	C33-C34	10 577	4930	15 507
Myeloid leukaemia (morphology 9840-9930)	C42	1366	1100	2466
Kidney	C64	1318	942	2260
Bladder	C67	3265	1047	4312
Central nervous system	C70–C72	1394	1115	2509
Thyroid	C73	762	3470	4232
Breast	C50	484	45 050	45 534
Vulva	C51	–	1059	1059
Vagina	C52	–	329	329
Cervix	C53	–	28 499	28 499
Uterine body	C54	–	3607	3607
Ovary (mucinous subtype)	C56	–	340	340
Penis	C60	1048	–	1048
Prostate	C61	23 991	–	23 991
Testicle	C62	1168	–	1168
Skin (comparison group)	C44	14 959	12 012	26 971
Total	–	105 718	125 384	231 102

ICD-O-3, International Classification of Diseases for oncology—third revision.

(18.6%). Breast and vagina was found with lower aetiological fractions (4.7%). In man, penis, testicles and prostate had fractions less than 10% (8.3%, 5.4% and 4.1%, respectively; data not shown). Stratification of the risk of developing cancer by gender showed that in men the highest risk was observed in the piriform sinus, bronchi and lung, hypopharynx, oropharynx and larynx (table 4). On the other hand, for women, the highest risk was for larynx, piriform sinus, bronchi and lung, oropharynx and oral cavity (table 5). With respect to specific cancers in men, low association was found for all sites analysed, except for cancers of the penis and testicles, which showed no statistically significant association with tobacco consumption (table 4). Among the woman specific cancers, the risk was considered to be moderate for cancers of the vulva, cervix and ovary and low for breast cancer. No statistical significance was found for cancers of the vagina and uterine body (table 5).

DISCUSSION

Although smoking is a well-established risk factor for the development of various types of cancer[3] the magnitude of the risk varies between studies according to race and income nation.[8] There are few national publications that summarise the magnitude of the risk of developing the disease in view of the specificities of the Brazilian population.

In Brazil, a survey conducted before the beginning of this study, covering urban and rural areas, estimated smoking prevalence at 34.8% (43.3% among men and 27% among women). Surveys carried out in subsequent periods have shown lower prevalence, which is consistent with the figures obtained among controls in the present study.[4]

We observed very strong association between tobacco and oral cavity cancer, oropharynx, hypopharynx, larynx and bronchi/lung. In a European study, which analysed 2103 cases of squamous cell carcinoma of the upper aero digestive tract[9] slightly lower values than those in the current study were found for cancers of the oral cavity and oropharynx and higher values for hypopharynx and larynx. In a meta-analysis involving 254 studies, a similar RR for laryngeal cancer, bronchi/lung and oral cavity were observed.[8]

When analysing the risk of developing cancer of the bronchi and lung according to gender, the present study

Table 2 Sociodemographic characteristics of the study population

	Cases						Controls					
	Total		Male		Female		Total		Male		Female	
Variables	N	Per cent	N	Per cent	N	Per cent	N	Per cent	N	Per cent	N	Per cent
Age (years)												
18–24	2134	1.0	803	0.9	1331	1.2	153	0.6	82	0.5	71	0.6
25–49	56 127	27.5	14 321	15.8	41 806	36.9	4761	17.7	2629	17.6	2132	17.7
50–64	73 748	36.1	34 658	38.2	39 090	34.5	7849	29.1	4629	30.9	3220	26.8
> 65	72 119	35.3	40 975	45.1	31 144	27.5	14 207	52.7	7618	50.9	6589	54.9
Race/skin colour												
White	108 095	59.0	50 489	61.8	57 606	56.7	20 068	80.6	11 119	80.6	8949	80.6
Black/brown	74 208	40.5	30 792	37.7	43 415	42.8	4751	19.1	2624	19.0	2127	19.1
Indian/yellow	955	0.5	431	0.5	524	0.5	83	0.3	50	0.4	33	0.3
Schooling												
Illiterate	21 482	14.6	8752	13.9	12 730	15.2	3183	15.8	1437	12.6	1746	20.0
≤8 years	97 588	66.5	43 747	69.7	53 811	64.1	13 538	67.2	7798	68.4	5740	65.6
>8 years	27 670	18.9	10 296	16.4	17 374	20.7	3427	17.0	2162	19.0	1265	14.5
Marital status												
With a partner	118 502	60.1	61 721	70.8	56 731	51.7	15 760	60.2	10 187	70.2	5573	47.7
Without a partner	78 551	39.9	25 448	29.2	53 103	48.3	10 436	39.8	4332	29.8	6104	52.3
Region of residence												
North	15 931	7.8	5533	6.1	10 398	9.2	1016	3.8	597	4.0	419	3.5
Northeast	34 334	16.9	12 431	13.7	21 903	19.4	4998	18.6	2857	19.2	2141	17.9
Centre west	4310	2.1	1734	1.9	2576	2.3	358	1.3	199	1.3	159	1.3
Southeast	94 134	46.3	42 973	47.5	51 161	45.3	12 452	46.4	6932	46.5	5520	46.2
South	54 765	26.9	27 767	30.7	26 998	23.9	8040	29.9	4320	29.0	3720	31.1
Smoking												
Yes	97 788	47.9	58 342	64.3	39 446	34.8	8344	30.9	6032	40.3	2312	19.2
No	106 343	52.1	32 417	35.7	73 926	65.2	18 627	69.1	8927	59.7	9700	80.8
Alcohol consumption												
Yes	51 752	29.2	38 698	48.1	13 054	13.5	4219	16.9	3600	26.3	619	5.5
No	125 684	70.8	41 716	51.9	83 968	86.5	20 750	83.1	10 106	73.7	10 644	94.5
Total	204 131	100	90 759	44.5	113 372	55.5	26 971	100	14 959	55.5	12 012	44.5

found a higher risk associated with tobacco consumption for the female population. However, a distinct result was described in a study involving the Japanese population, which showed an RR 4.39 times greater for men and 2.79 for women.[10]

In the present study, we found moderate association between smoking and nasopharyngeal cancer. Discrepant results were reported in studies of other populations. For example, after adjusting for age, gender, smoking, drinking and family history of cancer, a higher risk was observed in the Chinese population[11] while smoking conveyed no increased risk in an Italian population for undifferentiated subtypes of the disease but very high association for differentiated cases with consumption of more than 15 cigarettes/day.[12]

Moderate risk was also demonstrated in this study for cases of cancers of the nasal cavity, middle ear and sinuses compared with the general population and for gender. This result was also revealed in another study[13] that evaluated 14 563 patients and showed a moderate risk for the general population and for men and women. It is noteworthy that to our knowledge, no study has considered the risk of piriform sinus cancer alone, although the present study showed very strong association between tobacco use and the development of cancer in this site.

Regarding the digestive tract, an elevated risk associated with smoking was observed for oesophageal cancer with a moderate risk for cancer of the stomach and pancreas. A recent meta-analysis described a lower risk for oesophageal cancer and a similar risk for cancers of the stomach and pancreas.[8] In this study, a moderate risk was found in cancers of the anus and anal canal, but no publications discussing this association have been found. With regard to cases of cancer of the colon and rectum, the observed association was weak, which confirms the results of a review of 26 studies on the association between smoking and colorectal cancer.[14] Furthermore, the authors also reported an association only for rectal cancer and no association for colon cancer. Similar figures to those described here were found in a European study involving 2741 patients.[15] However, when the authors stratified by anatomic sites, proximal colon cancer showed an increased

Table 3 Association between smoking and the development of different types of cancer and aetiological fraction (AF) that can be attributed to smoking in both genders

Cancer site	Crude OR			OR adjusted*			
	OR	95% CI	p Value	OR	95% CI	p Value	AF(%)
Oral cavity	7.7	7.3 to 8.1	<0.001	4.3	4.0 to 4.5	<0.001	59.5
Oropharynx	12.0	10.8 to 13.3	<0.001	5.2	4.6 to 5.9	<0.001	68.1
Nasopharynx	2.4	2.1 to 2.7	<0.001	1.8	1.5 to 2.0	<0.001	22.9
Piriform sinus	19.2	15.1 to 24.4	<0.001	8.1	6.2 to 10.6	<0.001	78.5
Hypopharynx	13.4	11.6 to 15.5	<0.001	5.7	4.8 to 6.7	<0.001	70.7
Oesophagus	8.0	7.6 to 8.5	<0.001	4.0	3.7 to 4.2	<0.001	58.7
Stomach	2.6	2.4 to 2.3	<0.001	1.9	1.8 to 2.0	<0.001	25.3
Colon and rectum	1.3	1.3 to 1.4	<0.001	1.3	1.2 to 1.3	<0.001	8.5
Anus and anal canal	1.8	1.6 to 2.0	<0.001	2.1	1.8 to 2.3	<0.001	23.4
Liver	2.2	2.0 to 2.5	<0.001	1.4	1.2 to 1.6	<0.001	14.1
Gallbladder	1.2	0.9 to 1.5	0.621	1.3	1.0 to 1.6	0.03	7.4
Other parts of the biliary tract	1.8	1.4 to 2.2	<0.001	1.7	1.3 to 2.1	<0.001	18.2
Pancreas	1.9	1.8 to 2.1	<0.001	1.8	1.6 to 2.0	<0.001	20.7
Nasal cavity, middle ear and paranasal sinuses	2.5	2.2 to 2.8	<0.001	1.9	1.6 to 2.2	<0.001	24.9
Larynx	12.0	11.2 to 12.9	<0.001	6.3	5.9 to 6.8	<0.001	70.9
Bronchi and lung	9.3	8.8 to 9.7	<0.001	7.9	7.4 to 8.3	<0.001	70.4
Kidney	1.7	1.5 to 1.8	<0.001	1.6	1.4 to 1.7	<0.001	15.9
Bladder	3.5	3.3 to 3.7	<0.001	2.8	2.6 to 3.1	<0.001	39.1
Central nervous system	1.0	0.9 to 1.1	0.744	1.0	0.9 to 1.1	0.64	–
Thyroid	0.5	0.5 to 0.6	<0.001	0.8	0.7 to 0.8	<0.001	–
Myeloid leukaemia	1.0	1.0 to 1.1	0.213	1.0	0.9 to 1.1	0.91	–

*Adjusted for gender, age and alcohol consumption.

risk, whereas no significant increased risk was observed for distal colon cancer.

For neoplasms of the urinary tract, moderate association with smoking was found for cases of kidney cancer, with comparable figures in both genders. Similar findings were reported in a meta-analysis involving 24 epidemiological studies.[16] The authors stressed that the risk was proportional to tobacco consumption for both genders. Regarding the cases of bladder cancer, strong association was found with smoking with similar results in men and women. A case–control study involving 1586 patients showed a moderate risk of cancer, with increasing values for low-grade superficial, high-grade superficial or invasive tumours. Furthermore, women were at increased risk for invasive types when they consumed similar amount of cigarettes to men.[17]

Although the authors of the present study have not identified specific studies with reference to the association between smoking and gallbladder cancer, the current results point to weak association in the general population, although when stratified by gender, the association was not significant for men and was weak for women. With respect to liver cancer, one meta-analysis evaluated the association with tobacco smoking and its development, finding a moderate risk in this disease, which supports the IARC conclusion.[18] In the present study, we found a weak association, which corroborated the findings of a prospective cohort study conducted in Singapore with 394 patients with hepatocellular carcinoma.[19]

The results of this study showed no association between smoking and the risk of developing cancer of the central nervous system and myeloid leukaemia. Similar findings were shown in a prospective cohort study that highlighted a lack of association with brain tumours. However, the authors showed statistically significant association for myeloid leukaemia, in contrast to the results presented here.[20]

Male genital tract cancers have not been listed[2] as related to tobacco. A lack of association between these cancers and smoking was confirmed in the current study. For prostate cancer this study showed weak association with smoking. A large prospective cohort study found a decreased risk for non-advanced disease in current smokers, but an increased risk of fatal prostate cancer among smokers.[21]

In assessing the association between smoking and developing woman specific cancers, we observed a scarcity of publications that addressed this issue in some tumour locations. For breast cancer, despite the large number of studies, the association remains controversial. Although it is known that cigarettes contain carcinogens that can increase the risk of developing the disease, its antiestrogen action may be a protective factor. In the present study, we found a weak association between smoking and breast cancer, a finding which is supported by a study which evaluated 1240 women diagnosed with invasive breast cancer and reported that consuming 10 or more cigarettes/day for up to 20 years increases the risk of breast cancer by 34%.[22] In cases of cancer of the

Table 4 Association between smoking and the development of different types of cancer in men

Cancer site	Crude OR			OR adjusted*		
	OR	95% CI	p Value	OR	95% CI	p Value
Oral cavity	7.8	7.3 to 8.3	<0.001	4.4	4.1 to 4.8	<0.001
Oropharynx	10.2	9.0 to 11.6	<0.001	5.3	4.6 to 6.1	<0.001
Nasopharynx	2.1	1.8 to 2.4	<0.001	1.8	1.5 to 2.1	<0.001
Piriform sinus	14.1	10.8 to 18.3	<0.001	7.8	5.9 to 10.5	<0.001
Hypopharynx	11.1	9.4 to 13.1	<0.001	6.1	5.1 to 7.3	<0.001
Oesophagus	7.6	7.0 to 8.1	<0.001	4.0	3.7 to 4.3	<0.001
Stomach	2.5	2.3 to 2.6	<0.001	1.9	1.8 to 2.0	<0.001
Colon and rectum	1.4	1.4 to 1.5	<0.001	1.3	1.2 to 1.4	<0.001
Anus and anal canal	2.2	1.8 to 2.7	<0.001	2.1	1.6 to 2.7	<0.001
Liver	2.2	1.9 to 2.3	<0.001	1.4	1.2 to 1.7	<0.001
Gallbladder	1.6	1.1 to 2.2	0.012	1.4	0.9 to 2.1	0.13
Other parts of the biliary tract	1.9	1.4 to 2.5	<0.001	1.7	1.2 to 2.3	0.003
Pancreas	2.0	1.8 to 2.3	<0.001	1.7	1.4 to 2.0	<0.001
Nasal cavity, middle ear and paranasal sinuses	2.5	2.1 to 2.3	<0.001	2.0	1.6 to 2.4	<0.001
Larynx	8.8	8.2 to 9.5	<0.001	5.6	5.1 to 6.1	<0.001
Bronchi and lung	8.9	8.3 to 9.4	<0.001	7.7	7.2 to 8.3	<0.001
Kidney	1.6	1.4 to 1.8	<0.001	1.7	1.5 to 1.9	<0.001
Bladder	3.0	2.8 to 3.2	<0.001	2.9	2.7 to 3.2	<0.001
Central nervous system	0.9	0.8 to 1.2	0.104	1.0	0.9 to 1.2	0.54
Thyroid	0.7	0.6 to 0.8	<0.001	0.7	0.6 to 0.9	<0.001
Myeloid leukaemia	1.0	0.9 to 1.1	0.347	1.0	0.8 to 1.1	0.70
Penis	1.5	1.3 to 1.7	<0.001	1.2	1.0 to 1.4	0.06
Prostate	1.2	1.2 to 1.3	<0.001	1.1	1.1 to 1.2	<0.001
Testicle	0.7	0.6 to 0.8	<0.001	1.2	1.0 to 1.4	0.13

*Adjusted for age and alcohol consumption.

vulva and vagina, the association was moderate and low, respectively. No studies that address the relationship between smoking and the risk of developing cancer of the vulva and vagina have been identified. For cervical cancer, the risk was moderate, which is consistent with the review of 23 epidemiological studies involving 13 541 women, which found an increased risk for squamous cell carcinoma, although the same was not observed for adenocarcinoma.[23] Regarding ovarian cancer, only the mucinous subtype seems to be positively associated with tobacco use; in this study the association for this tumour type was moderate, confirming the observations of a meta-analysis of 910 women with mucinous and 5564 with non-mucinous ovarian cancer, in which a risk for mucinous cases and lack of association for other subtypes was found.[24] Among the remaining specific cancers in women, results of this study showed no association between smoking and the risk of developing cancer of the uterine body. However, even when considering the toxicity and carcinogenic effects of tobacco, the risk of endometrial cancer appears to be reduced. In another study, a protective effect of smoking was demonstrated with 28% reduction in the risk of endometrial cancer for women who consumed 20 or more cigarettes/day.[25] Furthermore, the association did not vary with menopausal status, oral contraceptive use or hormone replacement therapy. When considering postmenopausal women with a higher body mass index, the protective effect was even more noteworthy. A European multicenter study involving 249 986 female smokers, of whom 619 were diagnosed with endometrial cancer, also showed that tobacco consumption in postmenopausal women reduces the risk of disease, while moderate risk was found in premenopausal women.[26] Tobacco use appears to reduce the risk of developing thyroid cancer, but the actual mechanism of this association needs to be better understood. Protection was observed for both genders, similar to the results of a prospective study involving 1003 participants who found a protective effect of smoking with a 32% reduction in risk for the general population, 17% for men and 37% for women. Moreover, the authors reported a decreased risk for the papillary subtype and possibly for the follicular subtype.[27]

With regard to AF, a study with a similar design to that used here estimated the proportion of cancer cases related to exposure to tobacco and, in line with the results of the current study, showed values above 80% for most cancers of the respiratory tract, between 20% and 50% for digestive tract and lower urinary cancers.[13] A Brazilian study also assessed the population attributable risk between smoking and developing some types of cancers and reported that the total elimination of smoking would reduce the risk of oesophageal cancer by 54%, of lung cancer cases by 71%, and of cancer of larynx by 86%.[28]

Table 5 Association between smoking and the development of different types of cancer in women

Cancer site	Crude OR			OR adjusted*		
	OR	95% CI	p Value	OR	95% CI	p Value
Oral cavity	5.8	5.4 to 6.3	<0.001	4.2	3.8 to 4.7	<0.001
Oropharynx	8.5	6.9 to 10.4	<0.001	5.3	4.2 to 7.8	<0.001
Nasopharynx	2.2	1.8 to 2.8	<0.001	1.8	1.4 to 2.4	<0.001
Piriform sinus	16.4	8.7 to 31.0	<0.001	9.6	4.5 to 20.5	<0.001
Hypopharynx	7.6	5.5 to 10.4	<0.001	4.4	3.0 to 6.4	<0.001
Oesophagus	6.3	5.7 to 6.9	<0.001	4.2	3.7 to 4.7	<0.001
Stomach	2.3	2.2 to 2.4	<0.001	1.8	1.6 to 2.0	<0.001
Colon and rectum	1.4	1.3 to 1.5	<0.001	1.2	1.1 to 1.3	<0.001
Anus and anal canal	2.7	2.4 to 3.1	<0.001	2.1	1.8 to 2.4	<0.001
Liver	1.9	1.5 to 2.3	<0.001	1.4	1.1 to 1.9	0.004
Gallbladder	1.5	1.2 to 1.9	<0.001	1.2	1.0 to 1.6	0.01
Other parts of the biliary tract	1.9	1.4 to 2.6	<0.001	1.7	1.2 to 2.4	0.004
Pancreas	2.1	1.8 to 2.5	<0.001	1.9	1.6 to 2.3	<0.001
Nasal cavity, middle ear and paranasal sinuses	2.3	1.8 to 2.9	<0.001	1.7	1.3 to 2.3	<0.001
Larynx	13.2	11.3 to 15.3	<0.001	9.8	8.3 to 11.7	<0.001
Bronchi and lung	9.6	8.9 to 10.4	<0.001	7.9	7.2 to 8.6	<0.001
Kidney	1.8	1.6 to 2.1	<0.001	1.4	1.2 to 1.7	<0.001
Bladder	3.0	2.6 to 3.4	<0.001	2.6	2.2 to 3.0	<0.001
Central nervous system	1.2	1.1 to 1.4	0.006	1.0	0.8 to 1.2	0.93
Thyroid	0.9	0.8 to 1.0	0.005	0.8	0.7 to 0.8	<0.001
Myeloid leukaemia	1.3	1.1 to 1.5	0.001	1.0	0.9 to 1.2	0.74
Breast	1.7	1.6 to 1.7	<0.001	1.2	1.2 to 1.3	<0.001
Vulva	2.5	2.2 to 2.9	<0.001	2.0	1.7 to 2.4	<0.001
Vagina	1.7	1.3 to 2.1	<0.001	1.2	0.9 to 1.7	0.27
Cervix of uterus	2.8	2.7 to 3.0	<0.001	2.0	1.9 to 2.1	<0.001
Uterine body	1.0	1.0 to 1.1	<0.001	1.0	0.9 to 1.1	0.54
Ovary (mucinous)	2.2	1.7 to 2.7	<0.001	2.1	1.6 to 2.7	<0.001

*Adjusted for age and alcohol consumption.

A limitation of this study is that it is based on the analysis of secondary data, with data collected in a large number of cancer treatment centres, making it difficult to standardise data collection. Moreover, we observed a high percentage of missing values for some variables. Such potential sources of bias were minimised by the Brazilian NCI through the construction of a web-based information system, the formulation and distribution of a manual of routines and proceedings, and the training of medical record technicians in order to standardise the collection and inputting of information. In addition, in its current version, the Integrator CHR System does not store detailed information on smoking history, being impossible to estimate the total lifetime dose or total dose in pack-years. Another limitation is that we used as control non-melanoma skin cancers that may have different behaviours in cases and controls taking into consideration skin colour, ethnic origin and geographical precedence.

A strong point worth mentioning is that the association between smoking and cancer was adjusted for alcohol consumption, another important determinant of the risk of developing cancer. Even with these limitations, the opportunity to define the magnitude of the risk of developing cancer associated with tobacco use and the fraction of cancers that can be attributed to its consumption by a large Brazilian national study allowed, for the first time in the country, a comprehensive overview of this association.

In conclusion, this study confirms a high risk of developing cancer of the hypopharynx, bronchi and lung, larynx, oropharynx and oral cavity, oesophagus and bladder cancer among smokers and establishes the AF attributable to smoking in the development of different types of cancers in Brazil.

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