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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 (parotid 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.

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 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. Brazil has a mixed population composition with varied genetic, epidemiological and sociodemographic 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. 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 the 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...
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 the magnitude of the risk varies between studies according to race and income nation. 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.

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 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.

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

| Cancer site                  | ICD-O-3 | Male     | Female   | Total   |
|------------------------------|---------|----------|----------|---------|
| Oral cavity                  | C00–C08 | 9080     | 2078     | 11 158  |
| Oropharynx                   | C10     | 2458     | 2085     | 4 543   |
| Nasopharynx                  | C11     | 740      | 408      | 1 148   |
| Piriform sinus               | C12     | 651      | 240      | 891     |
| Hypopharynx                  | C13     | 1429     | 156      | 1 585   |
| Oesophagus                   | C15     | 6884     | 1943     | 8 827   |
| Stomach                      | C16     | 6861     | 4285     | 11 146  |
| Colon and rectum             | C18–C20 | 7813     | 1644     | 9 457   |
| Anus and anal canal          | C21     | 375      | 269      | 644     |
| Liver                        | C22     | 750      | 582      | 1 332   |
| Gallbladder                  | C23     | 129      | 225      | 354     |
| Other parts of the biliary tract | C24   | 199      | 96       | 295     |
| Pancreas                     | C25     | 918      | 472      | 1 390   |
| Nasal cavity, middle ear and sinuses | C30–C31 | 525      | 168      | 693     |
| Larynx                       | C32     | 6574     | 1191     | 7 765   |
| Bronchi and lung             | C33-C34 | 10 577   | 5930     | 16 507  |
| Myeloid leukaemia (morphology 9840-9930) | C42    | 1366     | 1100     | 2 466   |
| Kidney                       | C64     | 1318     | 942      | 2 260   |
| Bladder                      | C67     | 3265     | 1047     | 4 312   |
| Central nervous system       | C70–C72 | 1394     | 1115     | 2 509   |
| Thyroid                      | C73     | 762      | 3470     | 4 232   |
| 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.
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. 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 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. 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 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. 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. 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. However, when the authors stratified by anatomic sites, proximal colon cancer showed an increased

| Table 2 Sociodemographic characteristics of the study population |
|---------------------------------------------------------------|
| Variables           | Cases Total | Male | Female | Controls Total | Male | Female |
|                    | 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 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               | 108 995 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 | 4323 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 29.7 | 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 | 20 760 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 |
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* | AF(%) |
|-------------------------------------|----------|--------------|-------|
|                                     | 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  |
| Piriiform 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. 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.

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. 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 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.

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
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. 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 5,564 with non-mucinous ovarian cancer, in which a risk for mucinous cases and lack of association for other subtypes was found. 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 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. 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 1,003 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.

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  |
| Piniform 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.

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

| Cancer site                              | Crude OR | OR adjusted* | p Value | OR adjusted* |
|------------------------------------------|----------|--------------|---------|--------------|
| Oral cavity                              | 5.8      | 4.2          | <0.001  | 4.2          |
| Oropharynx                               | 8.5      | 5.3          | <0.001  | 4.2          |
| Nasopharynx                              | 2.2      | 1.8          | <0.001  | 1.8          |
| Piniform sinus                           | 16.4     | 9.6          | <0.001  | 9.6          |
| Hypopharynx                              | 7.6      | 4.4          | <0.001  | 4.4          |
| Oesophagus                               | 6.3      | 4.2          | <0.001  | 4.2          |
| Stomach                                  | 2.3      | 1.8          | <0.001  | 1.8          |
| Colon and rectum                         | 1.4      | 1.2          | <0.001  | 1.2          |
| Anus and anal canal                      | 2.7      | 2.1          | <0.001  | 2.1          |
| Liver                                    | 1.9      | 1.4          | <0.001  | 1.4          |
| Gallbladder                              | 1.5      | 1.2          | <0.001  | 1.2          |
| Other parts of the biliary tract         | 1.9      | 1.7          | <0.001  | 1.7          |
| Pancreas                                 | 2.1      | 1.9          | <0.001  | 1.9          |
| Nasal cavity, middle ear and paranasal sinuses | 2.3  | 1.7          | <0.001  | 1.7          |
| Larynx                                   | 13.2     | 9.8          | <0.001  | 9.8          |
| Bronchi and lung                         | 9.6      | 7.9          | <0.001  | 7.9          |
| Kidney                                   | 1.8      | 1.4          | <0.001  | 1.4          |
| Bladder                                  | 3.0      | 2.6          | <0.001  | 2.6          |
| Central nervous system                   | 1.2      | 1.0          | <0.001  | 1.0          |
| Thyroid                                  | 0.9      | 0.8          | <0.001  | 0.8          |
| Myeloid leukaemia                        | 1.3      | 1.0          | <0.001  | 1.0          |
| Breast                                   | 1.7      | 1.2          | <0.001  | 1.2          |
| Vulva                                    | 2.5      | 2.0          | <0.001  | 2.0          |
| Vagina                                   | 1.7      | 1.2          | <0.001  | 1.2          |
| Cervix of uterus                         | 2.8      | 2.0          | <0.001  | 2.0          |
| Uterine body                             | 1.0      | 1.0          | <0.001  | 1.0          |
| Ovary (mucinous)                         | 2.2      | 2.1          | <0.001  | 2.1          |

*Adjusted for age and alcohol consumption.
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