Relation between the Tobacco Epidemic and the recent COVID-19 Epidemic: a Current Overview of the Scientific Evidences

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Relação entre a Epidemia de Tabagismo e a Epidemia recente de Covid-19: um Panorama Atual das Evidências Científicas

Relación entre la Epidemia de Tabaquismo y la reciente Epidemia de Covid-19: una Visión General Actual de la Evidencia Científica

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INTRODUCTION

Tobacco epidemic killed nearly 100 million people in the XX century[1], it kills around eight million people annually worldwide and, in Brazil, it is associated to pain and suffering with the death of 156 thousand individuals per year[2]. In addition, in a country with expressive lack of resources to meet health emergency issues caused by the severe acute respiratory syndrome coronavirus 2 – Sars-CoV-2, approximately 57 billion Reais are spent annually in loss of productivity and direct cost with treatment of smokers. The critical evaluation of the existing scientific literature about the additional impact the tobacco epidemic may have over the coronavirus disease 2019 – (COVID-19) epidemic, and vice-versa, is the main goal of this article.

The first studies published about the association between smoking and being infected and/or evolve to severe respiratory complications in patients with COVID-19 came from China where the epidemics started first. The main results available until April 2020 were systematized by Szklo[3]. However, with the advance of the pandemic, new studies brought evidences for better understanding the association between tobacco use and COVID-19.

DEVELOPMENT

Tobacco and covid-19 health complications

The first systematic review about this topic published in March 17, 2020 brought the information that no association existed between smoking and severity of COVID-19[4]. However, the interpretation of the statistical tests utilized[5] was criticized and reanalyzed by other authors, since they found flaws in data extraction[6]. The reanalysis verified that the odds of smokers presenting worse progression of the disease was more than twofold than the odds of non-smokers (*odds ratio* – OR: 2.20; CI.95%: 1.31-3.67).

On April 15, 2020 a new systematic review with meta-analysis of the studies published in indexed journals until March 22, 2020 was published, addressing the relation of smoking (or chronic obstructive pulmonary disease – COPD) with severity or worse outcome of COVID-19[7]. This time, those studies who have not been contemplated in the former meta-analysis[4] were included and outcomes related to severity (that is, pneumonia), and/or to the use of Intensive Care Unit (ICU) and/or mechanic ventilation, and/or death were addressed. And the result indicated that smokers had twofold the odds of presenting worse severity/worse diagnosis when compared to non-smokers (OR 1.98; CI95%:1.29-3.05). And in patients with COPD, this relation was even stronger (OR 4.38; CI95%: 2.34-8.20).

Still about the analysis of the outcome of patients with COPD and/or smoking behavior, another systematic review was published meanwhile[8], with data from researches published until March 24. This analysis demonstrated that smokers had risk of mortality 38.5% higher than non-smokers; furthermore, the risk of COVID-19-related severe complications in smokers was 45% higher than the risk observed in non-smokers (relative risk - RR 1.45; CI95%: 1.03-2.04).

In another literature review followed by meta-analysis[9], the authors searched until April 28 and analyzed 19 studies about this same topic (1 from Korea, 2 from USA and 16 from China). Consistent with the findings of systematic review and meta-analysis articles published until then,

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they found odds approximately twofold of patients with tobacco history (smoker and ex-smoker) to evolve to a more unfavorable outcome when compared to the odds of non-smokers (OR 1.91; CI95%:1.42-2.59). The authors also conducted a sensitivity analysis with current smokers only (five studies of the 19 initially selected) and found similar results (OR 1.91; CI95%:1.10-3.29).

A research conducted only with cancer patients (active or past) from USA, Canada or Spain who were infected with the virus Sars-CoV-2, enrolled in the COVID-19 and Cancer Consortium (CCC19), analyzed the mortality after 30 days of COVID-19[10] confirmed diagnosis. Despite the low proportion of active smokers in this population (5%), considering that many of these patients must have quit smoking after being diagnosed with cancer, the results showed that 35% of ex-smokers among 928 patients analyzed also had higher odds of mortality when compared to non-smokers, regardless of gender, age and obesity (OR 1.60;CI95%:1.03-2.47).

And on May 1, 2020, it was published a peer-reviewed study involving patients of 169 hospitals in China, Japan, South Korea, Italy, Turkey, Spain, Germany, France, United Kingdom and USA with 8,910 individuals[11]. Once again, the results indicated that current smoker hospitalized had higher odds of dying than non-smoker or ex-smoker (OR 1.79; CI95%:1.29-2.47). This finding was independent from age, gender, preexisting selected comorbidities (for instance, cardiovascular diseases, COPD, etc.) and medications received during hospitalization. The study brought supplementary analyzes where it was observed that, when the data of middle income countries were grouped (China and Turkey), the odds of progressing to death were nearly threefold for smokers when compared to non-smokers; that is, a difference between the odds of the smoker and non-smoker considerably higher than what was verified for patients originated from European and North America high income countries. This finding suggests that hospital management of smoker patients with COVID-19 in poor resources countries can involve challenges even bigger (or yet, the management in general, because, for example, the risk of death among patients with cardiovascular disease was also higher in patients living in middle income *versus* high income countries). For instance, the difference of the general health condition among smokers and non-smokers can be even bigger in countries with predominance of social inequities. However, it is worth mentioning that on June 2, 2020 the authors asked to retract this article from the journal[12], because they informed that not all the authors had access to the full database, not being possible therefore to validate the results for auditing.

Still about the relation between tobacco and progression of COVID-19, a study published with data of 1,007 patients from three hospitals in Wuhan, China, hospitalized with mild (without any abnormality in imaging test) and moderate symptoms (mild symptoms and alterations in the imaging test) revealed that individuals with tobacco history had risk of evolving to severer outcomes of COVID-19, including death, nearly 46% lower than the risk of non-smokers (hazard ratio: HR 0.56; CI95% 0.34-0.91)[13], counterposing the entire literature available so far. The authors did not specify, however, the proportion of smokers and non-smokers who presented mild and moderate symptoms, respectively, which can influence the evaluation of the negative evolution of the disease.

Regarding the prevalence of tobacco among COVID-19 patients, a new systematic review and meta-analysis paper was published on May 9, 2020 and found low proportions of smokers among hospitalized patients, ranging from 1.4% (CI95%:0.0-3.4%) to 12.6% (CI95%:10.6-14.6%)[14], following the same line of the review that preceded it[15]. New studies addressing behavior changes of smokers during the COVID-19 epidemic, minimization of the possibility of selection and information biases, and discussions about the biological mechanisms of action of nicotine in the Sars-Cov-2 process of infection have been published recently. These studies allow us to interpret critically this finding, apparently contradictory of the low proportion of smokers infected *versus* the increased odds and/or increased risks of progression to unfavorable outcome of COVID-19 among smokers when compared to non-smokers.

Behavior change

A study conducted via internet with users scattered all over the United States attempted to understand the behavior changes of conventional cigarettes and e-cigarettes users during the pandemic[16]. It was observed that their reactions were very similar. Approximately 25% reduced and 30% increased their use. Nearly 35% were more and 15% were less motivated to stop smoking. In addition, 20% of the smokers reported having attempted once to stop smoking and reduce the risks associated to COVID-19 pandemic and 25% reduced the access to tobacco (*versus* 25% who increased the access). These results demonstrate that it is reasonable to expect behavior changes of the different types of smokers either for protection or on how to cope with more stress and confinement because of the pandemic restraining measures[17].

An internet-based study published with data from five countries (USA, Italy, South Africa, India and United Kingdom) in lockdown, but keeping its specificities (for instance, in South Africa, tobacco products sales were

banned), found that, in general, the pattern of "frequency of use" varied because of different situations experienced by the smokers[18]. In Italy and India, for example, smokers reported they were smoking more in-house. The desire to stop smoking increased if a close relative was infected by the COVID-19 virus. Compared to the previous study quoted conducted in the United States[16], it was reported a higher percentage of attempts to stop smoking. There was more demand to stockpile cigarettes (that is, to purchase) fearing the product could end and/or the stores would be included in the lockdown-mandated restrictions.

Results disclosed[19] of a health survey with approximately 45,000 Brazilian adults using a virtual questionnaire to evaluate behavior changes after the coronavirus pandemic arrived in the country revealed that about half of the smokers continued smoking the same quantity of cigarettes. However, while 12.2% reduced the quantity smoked, the remaining (34.4%) started to smoke more. The raise of the quantity of cigarettes smoked was bigger among women (*versus* men) and in individuals with complete elementary school or less (*versus* those with higher education level). There was no information available about quit attempts and/or motivation to stop smoking.

In Poland, a cross-sectional study conducted with a representative sample of the population (n=1,097) found that nearly 45% of the smokers interviewed were smoking more than before the beginning of the COVID-19 pandemic and 40% did not change their patterns of use[20]. This growth was unrelated to age, Body Mass Index (BMI), gender, education level or place of residence.

Another study[21] conducted online about the same topic, behavior change, with more than 2,000 students of three Italian universities attempted to understand four possible situations: (1) students who never smoked and continued not smoking; (2) students who used to smoke and continued smoking; (3) non-smoking students who started smoking and (4) smokers who quit smoking. And despite the difference of scope of the questions in relation to the United States study[16], the results encountered were a little different and showed that the great majority of these students remained in the same condition they were before the epidemic started, that is, 58.3% in condition (1) and 34% in condition (2). In addition, 2% started to smoke and 5.7% quit smoking.

Still about the Italian population, an online questionnaire sent to a representative sample of internet users aged 12 years or older found that among the 3,533 respondents, 3.3% quit smoking and 0.5% who smoked more than ten cigarettes (it does not specify whether per day, month, etc) started to smoke less[22]. However, the authors provided no information about the motivation to start or increase smoking that most likely occurred as well.

Finally, another study conducted by the Italian Anti-Smoking League with 1,825 participants who were not necessarily smokers, but revealed a percentage of non-smokers of only 30% and of ex-smokers of only 16%, attempted to understand how smokers of different types of products (conventional, electronic cigarettes, heated tobacco and dual use) changed their smoking behavior (quantity, purchase and thinking of quit smoking)[23]. Dual users of conventional and electronic cigarette or only conventional cigarette users reported a small reduction in their smoking. Exclusive conventional cigarette smokers, different from exclusive electronic cigarette users, reported they were thinking more often about quitting. However, they referred they tried to store/buy larger quantities of cigarettes. One third of ex-smokers considered resume smoking, while for those who never smoked, there was no "increased intent towards smoking".

In China, a study conducted with 6,416 individuals about behavior changes during COVID-19 pandemic[24] found that 25% of ex-smokers who responded to an online questionnaire reported having relapsed and resumed smoking. Furthermore, 20% of the population of smokers studied revealed they increased the frequency/quantity of cigarettes smoked. Near 2% of non-smokers before the epidemic started to smoke during the epidemic. On the other hand, 8.4% of smokers before the epidemic reported they quit smoking, a fraction well lower when compared to the quantity of smokers/individuals who relapsed or started smoking or increased the exposure (quantity) during the epidemic.

In the Australian population of 18 years or older, a behavior change study found that, during the period of epidemic where the country was in partial lockdown (maximum of five persons in marriages and funerals, restricted access but not forbidden in parks, etc.), social distancing and travel limitations, most of the individuals did not change their smoking behavior, including frequency or smoking status (89.7%)[25]. Negative changes occurred in 6.9% and positive changes in 3.4% of the interviewees. Among smokers, only 16.3% reported positive change, and 49.9% increased the use of cigarettes. This study also revealed that the main motives that led to negative changes in the smoking behavior were symptoms of depression, anxiety and stress.

With the Google Trends tool, a study attempted to understand whether the volume of consultations about smoking cessation had changed between January 9 and April 6, 2020. The result indicated that, despite the interest in COVID-19 and hands washing had increased in the period studied, quit smoking did not change[6].

And a research that evaluated the behavior change of the smoker through the increased use of a quite popular

UK applicative to help smokers to quit smoking found that the use of this applicative did not increase when COVID-19 epidemics spread throughout the United Kingdom[27].

The Japanese population was evaluated through a research with representative sample of the population (n=11,342) about the compliance with governmental guidelines (that is, it was not mandatory) to prevent COVID-19 spreading in the country, consisting, among other aspects, in respecting social distancing by avoiding poor ventilated closed places and/or places with agglomeration of persons without proper distancing and/or places where there is more proximity among individuals[28]. Although nearly 90% of the participants reported they knew the guidelines through TV news and/or internet, the odds of not complying (totally or partially) with the prevention recommendations for epidemic containing was 53% higher in smokers (daily or occasional), mainly females, than in non-smokers.

Differential selection and information biases among smokers and non-smokers

A study conducted among persons who were submitted to the coronavirus test (reverse-transcriptase polymerase chain reaction – RT-PCR) in a general care outpatient unit in Oxford, England found that active smokers had half the odd of testing positive when compared to non-smokers (OR 0.49; CI95%:0.34-0.71)[29]. Nevertheless, since smokers cough and have respiratory problems in general, it may have occurred higher probability of selecting smokers in general for testing, including a portion who did not have the virus, when compared to non-smokers selected to be tested and that could, actually, have more probability of being infected, which would be a selection bias.

An article published[30] about individuals who spontaneously went to the emergency service of Mount Sinai Hospital in New York with 21 to 50 years old (that is, proxy of the populational sub-group of the region under the hospital area of influence and that had no problem of access to health services) and tested positive for COVID-19 found that the odds of presenting initial x-ray evaluation that made them to be hospitalized by COVID-19 was 80% higher in smokers than in non-smokers. A small detour on the topic of the relationship between smoking among young people and COVID-19 suggests an increase in published articles on the importance that the use of electronic nicotine delivery systems (ENDS) may have for this population subgroup[31,32]. Despite there is no study so far that has measured the relation between the use of ENDSs and COVID-19 unfavorable outcomes, also because of the low proportion of adults users of ENDSs, there is a biological plausibility, supported by recent past examples of the relation of ENDSs use with other severe respiratory diseases, that these users may occasionally experience the same outcomes of conventional cigarettes smokers[31-33].

On May 23, the results of a study conducted in the United Kingdom[34], with information about lifestyles (including smoking) of nearly 400 thousand individuals stored in a great database and collected before the beginning of the COVID-19 epidemic (which minimizes the possibility of information bias) were published. These information were crossed with the results of the coronavirus positive tests of individuals with COVID-19 severe respiratory symptoms. Thus, it was possible to understand the proportion of smokers of the initial population (9.7% of active smokers) who evolved to hospitalization by COVID-19 severe symptoms (11.9% of active smokers), which, in a certain way, brings a unique possibility of comparison among hospitalized patients and baseline population that gave origin to severe cases of hospitalization by COVID-19. This potential of comparison is reinforced because the origin population of the cases has a proportion of active smokers lower than expected for the United Kingdom, in addition of higher socioeconomic and education level[35]; this, in a certain manner, allows to minimize a potential problem raised in previous studies related to less access to health services, mainly among low education smokers. The study found that, regardless of age, gender and other lifestyle-related risk factors, smokers had higher risks of being hospitalized by COVID-19 than non-smokers (relative risk – RR: 1.42; CI95%:1.12, 1.79); and when adjusted by age, gender, race and other comorbidities, this risk remained high (RR:1.36;CI95%:1.08, 1.71). The risks related to hospitalization by COVID-19 severe symptoms of ex-smokers were also higher than the risks of non-smokers. With this information of relative risks of smokers and ex-smokers (*versus* non-smokers) in the population studied and considering the expected prevalence of active smokers and ex-smokers in the general population (17% and 25%)[35], the authors estimated at 13.3% the attributable-fraction to hospitalization by COVID-19 severe symptoms in England because of tobacco use. When using also the respective information of physical inactivity and obesity, they reached an attributable fraction of 51% for these three unhealthy behaviors. Despite of i) this population attributable fraction may have been slightly overestimated because of the relative risks having been calculated from an observational study with more potential of biases than an intervention study (even considering the risks adjusted by innumerous confounding variables); and ii) having also utilized the relative risks obtained for a population that can have exposure levels to risk factors *per se* (frequency and

quantity) unlike those of the general population, it still gives a good idea of the importance of behavior risk factors for the evolution of the COVID-19 related outcomes.

Still in the same topic about what can be expected on the impact of the proportion of risk factors for hospitalization due to COVID-19 severe symptoms in a certain population, a study conducted in Brazil[36] estimated that 54.4% (CI95%: 53.6-55.2) of the Brazilian population presents at least one risk factor for the severe form of COVID-19 (65 years or older, cardiovascular disease, diabetes, hypertension, COPD, smoking, chronic renal disease, asthma, cancer and obesity). This corresponds to approximately 86 million Brazilians with high risk of presenting severer forms of the disease.

A representative study of the Italian population[37] designed to detect possible COVID-19 health-related symptoms the interviewees presented three weeks before the date of the interview (for example, fever, headache, cough, gastrointestinal disorders) found that the odds of presenting COVID-19 symptoms was 62% higher in smokers than in non-smokers (OR 1.62; CI95%:1.24-2.11), regardless of gender, education level and area of residence. An obvious limitation of this article is that part of these symptoms can reflect the infection by another virus (for example, influenza) and this may have been differentially distributed between smokers and non-smokers.

A cross-sectional study with information collected from a representative sample of the Polish population who had COVID-19 but did not need to be hospitalized (1,942 individuals)[38], found a proportion of smokers (11.2%) that would be half of the proportion expected for the origin population of the cases (21%). Considering, however, that in Poland every Sars-CoV-2 case needs to be reported to a reference physician who is responsible for deciding whether an in-house isolation or hospitalization is required, smokers with mild/moderate symptoms of COVID-19 may have had higher likelihood than non-smokers of having been referred to the hospital (selection bias).

Protective effect of nicotine?

Unlike the most plausible biologic justification that smokers present greater expression of the ACE2 enzyme, a receptor known as being associated to COVID-19[33,39,40], a French study[41] recently uploaded in an open platform, that does not go through peer review, raised the hypothesis that nicotine could play a protective role in the coronavirus infection with great impact in the media. The referenced study attempted to explain this hypothesis based in the argument that the coronavirus infection involves cells acetylcholine nicotine receptors that could be engaged in the inflammatory syndrome that accompanies the disease and that nicotine could prevent and control the syndrome. And based on this hypothesis, other articles started to be published about the importance of using nicotine as a form to prevent and treat COVID-19[42-44]. Another study[45] brought the hypothesis that the constant exposure to smoke, which leads to a systemic attenuation of the smoker's defensive immune response could, paradoxically, make the excess of production of pro-inflammatory molecules (for example, cytokines), from the exposure to the COVID-19 virus to be more easily/strongly triggered in a "perfectly immunocompetent" individual as the non-smoker.

The National Cancer Institute José Alencar Gomes da Silva (INCA), it is worth mentioning, published a note[46] strongly criticizing the French study and the hypothesis that nicotine would play a protective role in the COVID-19 epidemics. The note warned about the risks of nicotine to the population health and the necessity, particularly in this period of pandemic, to reach the most vulnerable smoking population through effective public policies targeted to fight tobacco epidemic[3,40,47-50]. With attitudes like this, it is attempted, somewhat, to minimize also the interference of the tobacco industry in the perpetuation of the damages caused by these two epidemics[51].

CONCLUSION

The results of these new evidences reinforce the necessity of continuing to study the profile of the patients with COVID-19 in countries in different stages of the tobacco epidemic (including dissimilar scenarios of fighting tobacco adapted to distinct stages of the COVID-19 epidemic). This article is appropriate exactly when Brazil moves rapidly in the COVID-19 epidemic and that an important national study has found that vast majority of smokers is not reducing cigarette consumption, which, in a certain angle, concurs with the international findings. In addition, the updating of the specialized literature presented in this article confirms the scientific evidence of a worse outcome to the development of COVID-19 respiratory complications; moreover, this updating suggests that in researches with minimized selection and information biases, smokers would have higher risks of Sars-CoV-2 infection. A potential challenge is to stimulate smoke cessation and prevent its initiation in stressful situations, uncertainty in relation to the future and social isolation at home. For such, it is necessary also to recognize and act to minimize the interference of the tobacco industry in public policies reinforcing the negative impact of smoking-attributable health expenses.

CONTRIBUTIONS

André Salem Szklo and Neilane Bertoni contributed substantially for the conception and design of the study, gathering, analysis and interpretation of the data, wording, critical review and approval of the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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