# Original Article ●●●●

# Smoking influence on the skin quality of white women

*Influência do tabagismo na qualidade da pele de mulheres brancas*

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■ **ABSTRACT**

**Introduction:** This study aimed to evaluate the influence of smoking on the skin quality of Caucasian women by analyzing collagen, elastic fibers, and vascularization. **Methods:** Histological and morphometric analysis was carried out on the pre-auricular flaps of 78 women undergoing facial cosmetic surgery. The patients were paired (n = 39) based on age, to form a group of smokers and another of non-smokers. Collagen types I and III were quantified using Picrosirius Ultra red staining, Weigert staining was used to analyze elastic material, and anti-CD34 immunostaining highlighted blood vessels. **Results:** Dermal density of both types of collagen decreased with age in both groups. The decrease in type I was higher in the dermis of smokers aged 50-59 years (p = 0.019). Elastic material increased in the dermis with age, becoming fragmented, thickened, and disorganized, particularly in 50-59-year-old smokers (p = 0.006). Moreover, in smokers, a gradual and significant increase in the number of microcirculatory vessels also observed (p = 0.008). **Conclusion:** The skin of women who smoke contains less collagen (type I in particular), more degenerated, fragmented and thickened elastic material, and a greater number of blood vessels.

**Keywords:** Skin; Women; Collagen; Elastic tissue; Microcirculation; Smoking.

■ **RESUMO**

**Introdução:** Avaliar a influência do tabagismo na qualidade da pele de mulheres brancas analisando o colágeno, as fibras elásticas e a vascularização. **Métodos:** Realizou-se análise histológica e morfométrica de 78 retalhos pré-auriculares de mulheres brancas que se submeteram à cirurgia estética facial. As pacientes foram pareadas conforme a idade, constituindo dois grupos (n=39), um de fumantes e um de não fumantes. Utilizaram-se a coloração de Picrosírius Ultra red para quantificar os colágenos I e III, a coloração de Weigert para a análise do material elástico e o imunomarcador anti CD34 para evidenciar os vasos sanguíneos. **Resultados:** Foi possível verificar que em fumantes e não fumantes há diminuição da densidade de colágeno dérmico com o envelhecimento, tanto na fração I quanto na III. A diminuição da fração I é maior na derme de fumantes, na faixa etária de 50 a 59 anos (p=0,019). O material elástico aumenta na derme com o passar dos anos, tornando-se fragmentado, espessado

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e desorganizado, de modo mais acentuado na derme das fumantes, na mesma faixa etária (p=0,006) e, finalmente, existe um aumento gradativo do número de vasos na microcirculação, mais significativo nas fumantes (p=0,008). **Conclusão:** A pele de mulheres fumantes contém menos colágeno (especialmente do tipo I), mais material elástico degenerado, fragmentado e espessado e maior número de vasos sanguineos.

**Descritores:** Pele; Mulheres; Colágeno; Tecido elástico; Microcirculação; Tabagismo.

## INTRODUCTION

The complex process of healing, defined as "the closing of tissue failures or replacing the tissue destroyed with fibrous tissue or another that is equal, thus reassembling the injured portions," is essential for survival following trauma with tissue injury[1].

Smoking, along with several other factors, can negatively influence this process[2].

The synthesis of subcutaneous collagen is significantly inhibited in smokers[3]. Cadmium, a component of tobacco, has been associated with the inhibition of pro-collagen production by fibroblasts[4].

The association between smoking and healing impairment is well known in clinical practice, and is a reason for concern among plastic surgeons. Smoking has been related to higher risk of complications associated with healing such as skin necrosis, infection of the surgical site, dehiscence walls, thick scars, and delayed epidermal healing[5-8]. Experimentally, it was found that nicotine administration in rats increases the area of necrosis in skin flaps[9-11].

Maintenance of the endothelium and microcirculation integrity are required for nutrient transport and supply, as well as the removal of metabolites from tissues. It has been clinically shown that collagen deposition is directly and significantly correlated to oxygen tension and perfusion measures[12].

Nicotine has vasoconstrictor activity, reduces $pO_2$ in tissues, increases platelet aggregation, and diminishes the proliferation of macrophages and fibroblasts[13]. Fibroblasts require a $pO_2$ of 15mmHg for cell division and 15–30mmHg for collagen synthesis. This suggests that the vasoconstriction caused by nicotine may contribute to decreased oxygen tension and impair wound healing[13].

Exposure of dermal fibroblasts to tobacco has been linked with decreased synthesis of type I and III collagen[2,14–19]. Sorensen et al. observed in smokers a decrease in inflammation, contraction, fibroblast proliferation, and vitamin C[18–19]. In our line of research, studies carried out with rats receiving nicotine showed that collagen density was not affected, but did result in a decreased fibroblast population[20–21].

The catabolism of collagen is carried out by a series of proteolytic enzymes belonging to the metallo-proteinase (MMP) group, which are produced by fibroblasts and other cell types. Smoking has already been identified as interfering with MMP-1, MMP-2, MMP-3, MMP-7, and MMP-8[14,15,22]. Besides affecting the extracellular matrix, smoking has also been found to alter endothelial and fibroblastic function[23].

Nicotine's vasoconstriction effect has been questioned. According to Usuki et al., small doses of nicotine would result in increased skin blood flow[24], while Sørensen et al. reported that the administration of nicotine does increase blood flow, but that smoking decreases it by reducing tissue $pO_2$[18].

Chronic exposure to nicotine decreases the regulation of cholinergic nicotinic receptors in the endothelium and induces a reduction in the serum levels of vascular endothelial growth factor (VEGF), thus impairing angiogenesis. Acute exposure, in turn, seems to promote increased capillary density[25]. Therefore, low concentrations of nicotine could accelerate angiogenesis and, in this condition, improve remodeling and healing[26].

The relationship between skin aging and smoking was first described in 1856 by Solly[27]. In 1985 Model established criteria to define the "smoker face": salient wrinkles, sunken eyes with bony prominences, and atrophic/ grayish skin or plethoric skin[28].

There are two processes regulating skin aging: an intrinsic process, which consists of a slow degenerative mechanism present in all tissues and organs, and an extrinsic process, which is caused by exposure to a variety of agents, such as photo-exposure and smoking[29]. The intensity of ageing is related to both the number of cigarettes/day and to the smoking duration[30–32].

In the skin, the first clinical signs of aging are dryness, loss of firmness and elasticity, and the appearance of wrinkles, especially in photo-exposed areas. These are accompanied by histological changes that vary depending on the part of the skin being analyzed and the age of the individual[33]. Senile skin shows flattening of the dermal-epidermal junction, marked atrophy, and loss of elasticity in dermal connective tissues, associated with reduction and disorganization of extracellular matrix components, type I and III collagens, elastic fibers, proteoglycans, and glycosaminoglycans[16,33]. Raduan et al., considered tobacco as an independent factor involved in the appearance of skin wrinkles[34].

For a long time, aging has been related to oxidative stress, which is significantly accelerated by the smoking-related increase in free radical formation[35,36]. These processes can be further enhanced by external factors, such as UV light[35].

Baroni et al., reported that aging causes a reduction in the density, fragmentation, and a disorganization of dermal collagen. The authors observed an increased density of elas-

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tic material, but its disorganization led these authors to call it elastotic material and not elastic fibers[37].

Just et al., consider smoking as an independent factor for the increase of elastic fibers in the reticular dermis of skin that is not photo-exposed and as an additive factor for the aging of photo-exposed skin[38].

When searching for information about the influence of smoking on aging, we found major methodological problems, including small and inadequate samples, and the lack of control for interference factors.

## OBJETIVE

The aim of this study is to compare the skin quality of smoking vs. nonsmoking Caucasian women.

## METHOD

The study analyzed slides prepared for the investigation registered under the protocol number 0541.0.084.000-09 in CONEP and number 5430 in the Human Research Ethics Committee of the Pontifical Catholic University of Paraná, after approval under the protocol number 0003880/10.

All patients, a total of 250, were included in the study after having signed the informed consent form to authorize the use of pre-auricular skin flaps removed during facial plastic surgery. A questionnaire completed by the patients allowed us to identify smokers and non-smokers. Interference factors, such as hormone replacement therapy, use of corticosteroids or other medications, previous facial aesthetic treatment, and intense sun exposure were used as exclusion criteria.

The slides containing histological sections were stained with hematoxylin-eosin (HE) and Picrosirius-red. HE staining allowed for the recognition of general skin structures, and under polarized light Picrosirius-red was used to identify the density of type I and III collagen (the main constituents of this tissue). Weigert's hematoxilyn was used to identify elastic material, and blood vessels in the sections were identified through immunostaining with anti-CD34 antibody. Five fields of each section were analyzed, and the average density of collagen and elastic material was obtained by calculating the percentage of the area examined, and the average number of vessels was determined by counting the average vessels in the fields examined. Evaluation was performed using a blind experimental design, with the investigator being unaware of which samples belonged to which group. The Image Plus® 4.5 program for Windows® from Media Cybernetics was used for the analysis.

The data were tabulated and statistically analyzed.

The results are expressed as averages, medians, minimum and maximum values, and standard deviations. To compare groups defined by their age range, the Kruskal-Wallis non-parametric test was used. The non-parametric Mann-Whitney test was used to compare groups of smokers and non-smokers within each age range. For parametric results, we used the Student's t test. Values of $p < 0.05$ indicated statistical significance. The data were analyzed by the computational program Statistics v.8.0.

## RESULTS

When considering the inclusion criteria, we were able to pair 78 women out of our original sample of 250; 39 non-smokers and 39 smokers.

Allocated by age, we were able to study three subgroups of smokers and non-smokers. Nine pairs were observed in the 40-49 age group, 24 in the 50-59 age group, and six in the 60-69 age group. We were not able to study patients over the age of 70, as the sample size was insufficient to carry out analysis when excluding confounding factors.

The collagen density in the dermis decreased with advancing age in both groups, though not significantly in the non-smoking group ($p = 0.211$), and significantly in the smoking group ($p = 0.042$). When comparing smokers and non-smokers within the same age group, the difference was not significant (Table 1).

**Table 1.** Collagen density in the skin of smoking and non-smoking women

| Age group | Group | TOTAL COLLAGEN | | | | | | p value* |
|---|---|---|---|---|---|---|---|---|
| | | n | Average | Median | Minimum | Maximum | Standard deviation | |
| 40-49 | Smokers | 9 | 27.3 | 26.9 | 21.1 | 39.9 | 5.5 | |
| | Non-smokers | 9 | 32 | 25.5 | 20.9 | 44.8 | 9.8 | 0.605 |
| 50-59 | Smokers | 24 | 23.5 | 19.9 | 16.8 | 43.4 | 6.8 | |
| | Non-smokers | 24 | 26.4 | 26.9 | 11.7 | 36.6 | 5.5 | 0.059 |
| 60-69 | Smokers | 6 | 19.5 | 17.1 | 13.7 | 31.4 | 6.3 | |
| | Non-smokers | 6 | 20.4 | 20.9 | 11.2 | 29.5 | 8.1 | 0.818 |

*Teste não-paramétrico de Mann-Whitney, p<0,05

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A significant reduction in type I collagen was observed in the skin of non–smokers with advancing age (p = 0.033), an effect more pronounced in the skin of smoking women (p = 0.005)(Table 2).
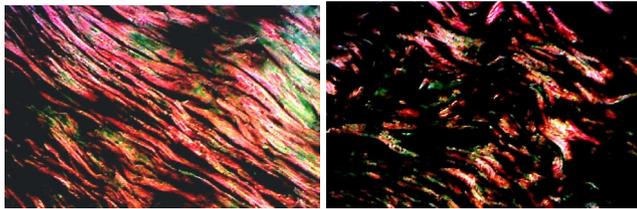
The analysis of the elastic material showed no significant difference in the skin of patients aged between 40 and 49 years (p = 0.071), though there is a significant increase in the skin of women aged 50–59 (p = 0.006), which is maintained

**Table 2.** Type I collagen density in the skin of smoking and non–smoking women

| Group | Age group | COL I | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | n | Average | Median | Minimum | Maximum | Standard devia-tion | p value* |
| Smokers | 40–49 | 9 | 14.9 | 13.9 | 12.8 | 22 | 2.9 | 0.033 |
| | 50–59 | 24 | 12.9 | 11.4 | 8.6 | 29.4 | 4.6 | |
| | 60–69 | 6 | 10.8 | 9.6 | 8.8 | 16.9 | 3.1 | |
| Non–smokers | 40–49 | 9 | 18.1 | 17.6 | 12.8 | 24.1 | 4 | 0.005 |
| | 50–59 | 24 | 14.4 | 14.8 | 6.4 | 18.9 | 3 | |
| | 60–69 | 6 | 11.6 | 12.3 | 6.8 | 14.9 | 3.1 | |

*Non–parametric Kruskal–Wallis test, p <0.05*

Although type I collagen density was lower in smokers, the within–age group comparison showed that collagen type I density was lower in the skin of smokers aged 40–49 (p = 0.077), and was significantly lower in smokers between 50 and 59 years of age (p = 0.019) (Table 3; Figure 1).

with increasing age (Table 5). Within–group analysis showed that the gain of elastic material in smoking patients aged 50–59 was not significant compared to that of their 40–49 year old counterparts (p = 0.401). However, this gain was significant when compared to the skin of patients aged between 60 and 69 years (p = 0.032). The same tendency was observed in the skin of non–smoking patients, although the overall percentage of elastic material in these women was lower; the skin of patients aged 40–49 did not have significantly different levels of elastic material compared to patients aged 50–59 (p=0.494). The comparison of women aged 50–59 with those aged 60–69 found a significant difference between the two groups (p = 0.044)(Figure 2).



**Figure 1.** *Photomicrographs of histological sections stained with Picrosirius–red, showing the skin section of a smoker (upper panel) and of a non–smoker (lower panel), aged between 50 and 59 years old (red = type I collagen and green = type III collagen)(200X).*

**Table 3.** Comparison of type I collagen density in the skin of smoking and non–smoking women of different age groups

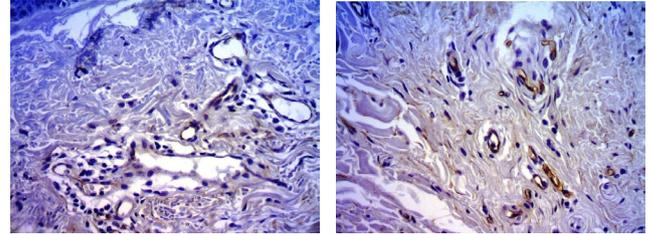| | | COL I | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Age group | Group | n | Average | Median | Minimum | Maximum | Standard devia-tion | P value* |
| 40–49 | Smokers | 9 | 14.9 | 13.9 | 12.8 | 22 | 2.9 | |
| | Non–smokers | 9 | 18.1 | 17.6 | 12.8 | 24.1 | 4 | 0.077 |
| 50–59 | Smokers | 24 | 12.9 | 11.4 | 8.6 | 29.4 | 4.6 | |
| | Non–smokers | 24 | 14.4 | 14.8 | 6.4 | 18.9 | 3 | 0.019 |
| 60–69 | Smokers | 6 | 10.8 | 9.6 | 8.8 | 16.9 | 3.1 | |
| | Non–smokers | 6 | 11.6 | 12.3 | 6.8 | 14.9 | 3.1 | 0.589 |
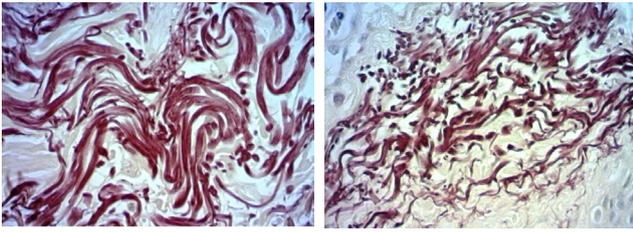
**Figure 2.** *Fotomicrografias de cortes histológicos de pele tratados pela hematoxilina de Weigert, a imagem superior, de paciente não fumante e a inferior de paciente fumante, da faixa 50 a 59 anos. (400X)*

Although type III collagen density diminishes with advancing age, this change was not significant in the skin of smokers and non-smokers (p = 0.124, and p = 0.526, respectively). The comparison between different age groups was also not significant (Table 4).

In smokers, the average number of vessels per field is higher in all of the evaluated age groups compared to non-smokers, and this increase is significant in the 50-59 age group (p = 0.008)(Table 6; Figure 3).



**Figure 3.** *Photomicrograph of skin sections of a non-smoker (upper panel) and a smoker (lower panel) in the 50-59 age group, stained with anti-CD 34 antibody (400X).*

**Table 4.** Type III collagen density in the skin of smoking and non-smoking women of different age groups.

| Age group | Group | COL III | | | | | | |
| | | N | Average | Median | Minimum | Maximum | Standard deviation | p value* |
|---|---|---|---|---|---|---|---|---|
| 40-49 | Smokers | 9 | 12.4 | 12 | 8.3 | 17.9 | 2.9 | |
| | Non-smokers | 9 | 13.9 | 10.2 | 7.8 | 23.5 | 6.4 | 0.863 |
| 50-59 | Smokers | 24 | 10.5 | 9.5 | 6.2 | 14.9 | 2.9 | |
| | Non-smokers | 24 | 12 | 11.8 | 5.3 | 17.7 | 2.8 | 0.106 |
| 60-69 | Smokers | 6 | 8.8 | 8.2 | 3.5 | 14.5 | 3.6 | |
| | Non-smokers | 6 | 8.8 | 9.5 | 2.3 | 14.6 | 5.5 | 1 |

*Non-parametric Mann-Whitney test, p <0.05*

**Table 5**. Average percentage of the area analyzed and occupied by elastic material, in different age groups

| Age group | Group | ELASTIC MATERIAL | | | | | p value* |
| | | n | Average | Minimum | Maximum | Standard deviation | |
|---|---|---|---|---|---|---|---|
| 40-49 | Smokers | 9 | 33.63 | 28.21 | 40.84 | 4.57 | |
| | Non-smokers | 9 | 30.03 | 25.19 | 34.58 | 3.12 | 0.071 |
| 50-59 | Smokers | 24 | 34.24 | 24.59 | 54.76 | 6.51 | |
| | Non-smokers | 24 | 30.06 | 19.18 | 38.75 | 5.24 | 0.006 |
| 60-69 | Smokers | 6 | 39.81 | 32.54 | 43.98 | 4.47 | |
| | Non-smokers | 6 | 34.40 | 27.57 | 43.58 | 5.58 | 0.047 |

*Parametric Student's t test, p<0.05*

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**Table 6.** Average number of vessels per field in the skin of smoking and non–smoking patients

| Age group | Group | VESSEL | | | | | | |
| | | n | Average | Median | Minimum | Maximum | Standard deviation | p value* |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Smokers | 9 | 8.0 | 8.3 | 5.3 | 10.4 | 1.5 | |
| 40–49 | Non–smokers | 9 | 6.8 | 6.4 | 3.4 | 10.5 | 2.3 | 0.297 |
| | Smokers | 23 | 9.1 | 9.0 | 7.1 | 12.5 | 1.3 | |
| 50–59 | Non–smokers | 24 | 7.9 | 8.0 | 3.9 | 9.9 | 1.4 | 0.008 |
| | Smokers | 6 | 9.1 | 8.7 | 6.4 | 12.4 | 2.0 | |
| 60–69 | Non–smokers | 5 | 8.1 | 8.4 | 5.6 | 9.9 | 1.7 | |

## DISCUSSION

Analyzing the results obtained in their studies, Baroni et al., concluded that skin aging induces qualitative and degenerative changes of the dermis, reduces type I and III collagen, as well as total collagen, and causes a disorganization and fragmentation of collagen fibers, especially from the age of 60 years[37]. Smoking impairs collagen synthesis by reducing the number of fibroblasts[2,3,14–21].

Broniarczyk–Dyla et al., stated that aging is accelerated in post–menopausal women due to a reduction in collagen and ovarian estrogen production[39].

It is expected that in addition to the physiological loss of collagen caused by aging, women smokers will show more pronounced loss. In this study, we observed that the skin of smokers had lower collagen levels, although the difference was not significant. However, collagen type I, which is structurally more organized, was lower in the skins of smokers aged 50–59 (p = 0.019). While this could not be confirmed in the other age groups, there was a tendency to have less collagen among smokers, though the sample was quite small. Although several authors have reported that dermal fibroblast exposure to tobacco decreases the synthesis of type I and type IIII collagen[2,14–19], this study found a reduction in both smokers and non–smokers, although this decrease was more pronounced in smokers.

The physiological elasticity and resilience of the dermis are due to elastic fibers[40]. Degeneration of elastic fibers, decrease in collagen, particularly type I collagen, and disorganization reduces the elasticity of the skin and enhances the formation of wrinkles[41].

Elastin network density increases from birth until it reaches its peak volume at around age 20 for women and age 40 for men[42]. With increasing age, the elastic fibers become thickened, tangled, degraded, and dysfunctional[43]. Biochemically, the elastotic material resembles elastin, although disorganized and abnormal in the ratio of various constituents[43]. In areas with actinic degeneration, the elastic fibers become thicker, with a progressive increase in the mass of abnormal granular elastotic material[41].

Smoking is considered an independent factor for the increase of elastic fibers in the reticular dermis of not photo–exposed skin, and as an additive factor for the aging of photo–exposed skin[38].

Ortolan's study reported that aging caused an increase in elastic material density, with quality modifications in the organization of elastic fibers[44]. Baroni et al., observed an increased density of elastic material, which was, however, disorganized, leading the authors to term it elastotic materials and non–elastic fibers[37].

In this sample, the skin dermis of smoking and non–smoking women showed an increase in elastic material density with age, which was particularly pronounced in the smokers. A very significant difference was detected in smokers belonging to the 50–59 age group (p = 0.006).

Longtime smokers frequently showed some degree of chronic obstructive pulmonary disease (COPD). Maclay et al. found increased elastin degradation in the skin of COPD–patients when compared to controls[45]. This report reinforces the previous findings regarding the disorganization and degradation of elastic fibers. Although Rosado et al. studied young adult male smokers (aged between 23 and 36 years old), they observed that elastic material increased 42.5% when compared to non–smoking controls[46].

Several authors have reported that aging promotes a decrease in cutaneous microcirculation with reduced capillary loops, vascular dilatation, and endothelial proliferation with de-

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creased functional reserve[47-49]. Studies in our line of research showed no significant changes in the blood vessel density of aging dermis[44]. In this study, we observed that the skin dermis of smokers contained a higher number of vessels, and this was very significant in the 50-59 age group (p=0.008). It is possible that a certain degree of tissue hypoxia stimulates neoangiogenesis.

Collagen synthesis and organization is dependent on oxygen[12], and so smoking could be considered to accelerate aging by interfering with collagen organization if nicotine promotes oxidative stress and vasoconstriction. Interfering factors greatly impair the study of this link in clinical practice. For example, most older patients present with age-related diseases and many use medication, both of which can interfere with collagen and vascularization. Moreover, many have already undergone one or even several rejuvenation treatments. Once exclusion criteria are applied, it becomes clear that very large samples are needed to ensure a sufficient number of patients for analysis. In this study, 250 women initially met the requirements for surgical treatment; however, once the exclusion criteria were applied, 68.8% of the sample was lost, and only 78 women remained. Caucasian women were primarily sampled due to their high density in the population of our region, and it is very likely that this behavior is different in women belonging to other racial groups. Girardeau et al., showed that there are differences in superficial epidermis, dermal functions, and cellular interactions between African and Caucasian skin[50].

In this cohort, we verified that aging decreases dermal collagen density, both types I and III, in smokers and non-smokers. However, this decrease is more pronounced in the dermis of smoking patients. Elastic material increases in the dermis over the years, becoming fragmented, thickened and disorganized, and this is more accentuated in the dermis of smokers, along with a gradual but significant increase in the number of microcirculatory vessels.

## CONCLUSION

The skin of women who smoke contains less collagen, particularly type I, and contains more elastic material that is degenerated, fragmented, and thickened, as well as a greater number of blood vessels.

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