ORIGINAL ARTICLE

Smoking is an Independent Marker of Poor Prognosis in Cutaneous Melanoma

Kalle MATTILA[1,2#], Helmi VIHINEN[3#], Antti KARLSSON[4], Heikki MINN[1], Pia VIHINEN[1] and Eetu HEERVÄ[1]
[1]Department of Oncology and FICAN West Cancer Centre, Turku University Hospital and University of Turku, [2]InFLAMES Research Flagship Center, University of Turku, [3]Turku School of Economics, University of Turku and [4]Auria Biobank and Turku University Hospital, Turku Finland. [#]These authors contributed equally to this paper.

Previous studies have suggested that persistent tobacco smoking impairs survival in cutaneous melanoma, but the effects of smoking and other prognostic factors have not been described in detail. This study examined the association of smoking (persistent, former, or never) with melanoma-specific (MSS) and overall survival (OS) in patients with cutaneous melanoma treated in Southwest Finland during 2005 to 2019. Clinical characteristics were obtained from electronic health records for 1,980 patients. Smoking status was available for 1,359 patients. Patients were restaged according to the 8th edition of the tumour-node-metastasis (TNM) classification. Smoking remained an independent prognostic factor for inferior melanoma-specific survival regardless of age, sex, stage, and comorbidities. The hazard ratio of death from melanoma was 1.81 (1.27–2.58, $p = 0.001$) in persistent and 1.75 (1.28–2.40, $p = 0.001$) in former smokers compared with never smokers. In 351 stage IV patients, smoking was associated with increased melanoma-specific and overall mortality: median MSS 10.4 (6.5–14.3), 14.6 (9.1–20.1), and 14.9 (11.4–18.4) months, $p = 0.01$ and median OS 10.4 (6.5–14.3), 13.9 (8.6–19.2), and 14.9 (11.7–18.1) months, $p = 0.01$ in persistent, former, and never smokers, respectively. In conclusion, since smoking represents an independent modifiable poor prognostic factor in patients with cutaneous melanoma, smoking habits should be proactively asked about by healthcare professionals, in order to support smoking cessation.

Key words: cigarette; melanoma; metastasis; skin cancer; smoking; survival.

Accepted Jan 4, 2023; Published Feb 7, 2023

Acta Derm Venereol 2023; 103: adv00860.

DOI: 10.2340/actadv.v103.3209

Corr: Eetu Heervä, Department of Oncology (Syöpäklinikka) Hämeentie 11, FIN-20521 Turku, Finland. E-mail: eetu.heerva@utu.fi

SIGNIFICANCE

Earlier studies have suggested that smoking impairs survival in patients with cutaneous melanoma, but the effect of smoking, along with other established prognostic factors, has not been described in detail. This study examined the association of smoking status (persistent, former, or never) with survival in patients with cutaneous melanoma treated in Southwest Finland in 2005 to 2019. Smoking was an independent prognostic factor for shorter survival after adjustment for other risk factors, including age, sex, TNM stage, and comorbidities. The detrimental effect of smoking on survival was most marked in patients with metastatic melanoma and these patients should routinely be supported to stop smoking.

Cutaneous melanoma is a growing health problem, especially in countries with fair-skinned populations, such as the Nordic countries (1, 2). According to the Finnish Cancer Registry the incidence of cutaneous melanoma has doubled in the 2000s (3). At the same time, survival rates are increasing, probably due to the increasing diagnosis of melanoma at an earlier stage (2, 4, 5). The most well-known risk factors for cutaneous melanoma are increased exposure to ultraviolet (UV) radiation, fair skin type, and genetic susceptibility (1). Epidemiological studies have shown a controversial inverse association between tobacco smoking and the incidence of cutaneous melanoma (2, 6–10). It has been suggested that smoking may protect from melanoma indirectly, by suppressing cutaneous inflammation (11, 12) and, directly, by affecting cell signalling pathways in melanocytes (12). Excess mortality from smoking may also cause survival bias, as patients who smoke die before developing cutaneous melanomas (7).

Established poor prognostic factors in cutaneous melanoma include increased Breslow thickness, ulceration of the primary tumour, and advanced TNM stage (tumour, node, and metastasis classification of malignant tumours) (1, 13). Older patients have worse prognosis than younger ones (14, 15). Men are diagnosed with more advanced melanomas and have higher mortality rates than women (4, 14, 15). Despite the fact, that melanoma is more common among people in higher socioeconomic classes, the mortality rate is higher in lower socioeconomic classes. This is probably due to a poorer lifestyle, including smoking habits, and poorer access to health services (4). Higher than normal body mass index (BMI) is thought to increase the risk of melanoma directly and indirectly through socioeconomic class (4, 9). The presence of comorbidities is also associated with more advanced stage of melanoma and shorter survival time (16).

Persistent smoking has been associated with increased melanoma-specific and overall mortality, but TNM staging was not included in these studies (17–19). Gibson et

al. (7) included stage as an explanatory covariate, and reported shorter overall, but not melanoma-specific, survival, in patients who smoke. We have previously reported increased mortality among males, but not females, with cutaneous melanoma who smoke compared with those who have never smoked (19). The aims of the current study were to explore the effect of smoking on survival and disease recurrence in a larger cohort of patients with melanoma with detailed information on other relevant prognostic factors, and to determine if smoking affects survival in stage IV patients.

MATERIALS AND METHODS

Study population

All patients with International Classification of Diseases 10th revision (ICD-10) code C43 or histopathological diagnosis of cutaneous melanoma during 2005 to 2019 were obtained from the electronic health records system of Turku University Hospital, representing good population-based coverage of the patients treated in Southwest Finland (19). Overall, 2,130 patients with cutaneous melanoma were identified. Patients with melanoma *in situ* (n = 119) and 31 patients whose TNM stage could not be determined were excluded to form the staging cohort (n = 1,980, Table SI). Smoking status could not be retrieved for 621 (31%) participants and these patients were excluded from further analyses. The remaining final patient cohort (n = 1,359) was manually restaged by the authors according to the 8th TNM classification (13). Patients with multiple primary melanomas (n = 3) were classified according to the first melanoma diagnosed within the study period.

Smoking status was determined based on the Universal Language Model Fine-tuning (ULMFiT) assisted deep learning natural processing algorithm from our previous study for patients diagnosed during 2009 or later, in which smokers and never smokers were correctly classified with high accuracy (accuracy 0.92) (19). The algorithm classifies smoking status (tobacco and cigars) over the whole observation period, and intermittent smokers are classified according to a probability logic of individual smoking entries, as described previously (19). Pack years and cessation years were seldom documented; thus, we cannot reliably distinguish cessation after melanoma diagnosis. Smoking status was obtained manually for those patients diagnosed during 2005 to 2008.

Patient data were completed manually by going through electronic health records to obtain patients' demographic characteristics, including age, sex, BMI, Eastern Cooperative Oncology Group (ECOG) performance status (where 0 denotes full independent performance status) (20), and Charlson Comorbidity Index (CCI) (where 0 denotes no comorbidities) (21) at melanoma diagnosis, and tumour characteristics, including Breslow thickness, ulceration, and *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) mutation status. At Turku University Hospital, *BRAF* mutation status was available only for stage III and IV melanomas and was determined using immunohistochemistry and PCR or next generation sequencing methods since 2008. Follow-up information on the course of melanoma (local melanoma recurrence, distant metastases, cancer treatments, last follow-up visit or death date, and cause of death (melanoma vs other)) was collected manually when available. Cause of death records were obtained from the national Statistics Finland registry.

Table I. Characteristics of 1,359 patients with known smoking status and 621 patients with unknown smoking status at the time of melanoma diagnosis

Smoking status	Never n = 841	Former n = 301	Persistent n = 217	p-value*	Unknown n = 621
Age, years, mean (range)	63 (11–94)	66 (23–90)	58 (16–93)	0.01	65 (5–101)
Age, years, median (IQR)	66 (55–76)	68 (60–76)	60 (50–70)	N.t	66 (53–79)
Age group, n (%)					
<45 years	123 (15)	29 (10)	39 (18)	<0.0001	81 (13)
45–70 years	392 (47)	141 (47)	128 (59)		270 (44)
>70 years	326 (39)	131 (43)	50 (23)		270 (44)
Sex, n (%)					
Female	470 (56)	77 (26)	91 (42)	<0.0001	309 (50)
Male	371 (44)	224 (74)	126 (58)		312 (50)
BMI, kg/m^2, median (IQR)	27 (24–30)	28 (22–34)	27 (24–30)	0.02	27 (24–30)
ECOG performance status, n (%)					
0	122 (32%	58 (32)	30 (28)	0.94	34 (23)
1	205 (53)	94 (52)	61 (57)		68 (47)
≥2	60 (16)	29 (16)	17 (16)		43 (30)
Unknown	454	120	109	N.t	476
Charlson Comorbidity Index, n (%)					
0	525 (62)	147 (49)	138 (64)	0.001	441 (71)
1	163 (20)	82 (27)	46 (22)		82 (13)
≥2	153 (19)	72 (24)	33 (15)		98 (16)
TNM Stage, n (%)					
I	478 (57)	140 (47)	116 (53)	0.01	405 (65)
II	167 (20)	67 (22)	33 (15)		113 (18)
III	121 (14)	60 (20)	38 (18)		80 (13)
IV	75 (9)	34 (11)	30 (14)		23 (4)
Breslow, mm, mean (range)	1.9 (0.1–20.0)	2.4 (0.1–18.5)	2.6 (0.2–30.0)	0.01	2.1 (0.1–30.0)
Breslow, mm, median (IQR)	1.1 (0.3–1.9)	1.5 (0.2–2.8)	1.1 (0.1–2.1)	N.t	1.0 (0.2–1.8)
Ulceration, n (%)					
No	466 (76)	152 (69)	111 (72)	0.15	347 (76)
Yes	150 (24)	68 (31)	43 (28)		108 (24)
Unknown	225	81	63	N.t	166
BRAF mutation, n (%)					
No	70 (52)	26 (54)	11 (37)	0.26	11 (29)
Yes	64 (48)	22 (46)	19 (63)		27 (71)
Unknown	707	253	187	N.t	583

IQR: interquartile range; N.t: not tested.
*Bonferroni-corrected χ^2 p-value test performed including persistent, former, and never smokers.

Ethics approval

The study was approved by the Institutional Review board of Turku University Hospital (license numbers T132/2019 and T206/2015). Informed consent was waived due to the retrospective design of the study according to Finnish legislation on secondary use of health data.

Statistical analysis

The primary endpoints of this study were melanoma-specific (MSS) and overall survival (OS) and the secondary endpoint was melanoma-free survival (MFS). MSS was defined as the time from melanoma diagnosis to death due to melanoma and patients who were alive or had died due to a non-melanoma cause were censored at the end of follow-up on 15 June 2021. OS was defined from melanoma diagnosis to death due to any cause. MFS was conditionally defined for completely resected, stage I–III patients as the time from primary melanoma diagnosis to disease recurrence (local or distant) at least 3 months after primary diagnosis. Descriptive variables were compared with Bonferroni-corrected χ^2 or analysis of variance (ANOVA) methods. Survival was analysed with Kaplan–Meier log-rank method. A multi-

variable Cox regression analysis was performed for MSS with enter method and 95% confidence intervals (95% CI). For the Cox regression analysis, age was dichotomized to ≤70 years and >70 years, as in our previous report (19). All analyses were made with SPSS version 27 (IBM Corp. Armonk, NY, USA). Statistical significance threshold was set at <0.05, applying SPSS-integrated Bonferroni correction to the alpha level.

RESULTS

Study population

Patient characteristics at the time of melanoma diagnosis are summarized in **Table I** for 1,359 patients with known smoking status and for 621 patients with unknown smoking status. Of 1,359 patients with known smoking status, 217 (16%) continued to smoke, 301 (22%) were former smokers, and 841 (62%) had never smoked. There was no change in the proportion of smokers over the study period of 15 years. Persistent smokers were more often men (58% vs 44%) and of younger age at the time of diagnosis (median 60 vs 66 years) compared with never smokers. Small differences in the stage of melanoma were observed according to smoking status, smokers presenting more often with stage III–IV disease. Comorbidities were most common among former smokers. Information on tumour ulceration and *BRAF* mutation status were not available for all patients, but their expression status was similar in all patient groups regardless of smoking status. In addition, 45 patients had received adjuvant treatment, usually interferon-alpha, after complete resection of stage III–IV melanoma.

Patient characteristics of 351 stage IV melanomas with known smoking status are shown in Table SII. A total of 168 (48%) patients had received systemic treatment for stage IV melanoma (51% of persistent smokers, 43% of former smokers, and 49% of never smokers). The proportion of women was largest (52% vs 19%) in never smokers. Age, BMI, ECOG performance status, Charlson Comorbidity Index, *BRAF* mutation status, metastasis stage, and the use of systemic treatment were evenly distributed in persistent, former and never smokers with stage IV melanoma.

Smoking increased the risk of death from melanoma independently of age, sex, and disease stage

With a median follow-up time of 4.9 years (range 0–16.0 years) for alive patients and when 622 deaths and 351 melanoma recurrences had occurred, smoking (persistent and former) was unequivocally associated with increased melanoma-specific and overall mortality (**Fig. 1** A, B), but only among former smokers with increased recurrence of melanoma (Fig. 1C). The unadjusted hazard ratio (HR) of death from melanoma was 1.76 (1.30–2.40) and 1.38 (1.03–1.85) and the unadjusted HR of any-cause death 1.56 (1.23–2.00) and 1.31 (1.04–1.65) in persistent and former smokers compared with never smokers, respectively (Fig. 1A, B). The estimated 5-year melanoma survival rates were 71% (persistent smokers), 76% (former smokers) and 83% (never smokers). The unadjusted HR of melanoma recurrence was 1.31 (0.99–1.75) in persistent smokers and 1.42 (1.11–1.82) in former smokers compared with never smokers (Fig. 1C). The MSS, OS, and MFS curves according to TNM stage regardless of smoking status are shown in Fig. S1.

In the multivariable Cox regression analysis, both persistent and former smoking were independently associated with short MSS while accounting for age, sex, TNM stage, and comorbidities (**Table II**). The adjusted HR of death from melanoma was 1.81 (1.27–2.58, $p=0.001$) in persistent smokers and 1.75 (1.28–2.40, $p=0.001$) in former smokers compared with never smokers, respectively. In addition to the smoking status, more advanced TNM stage ($p<0.001$) and older age ($p=0.001$) were also associated with inferior MSS in the multivariable analysis (Table II).

Overall, men presented more commonly with a history of smoking, stage III–IV disease, comorbidities, and

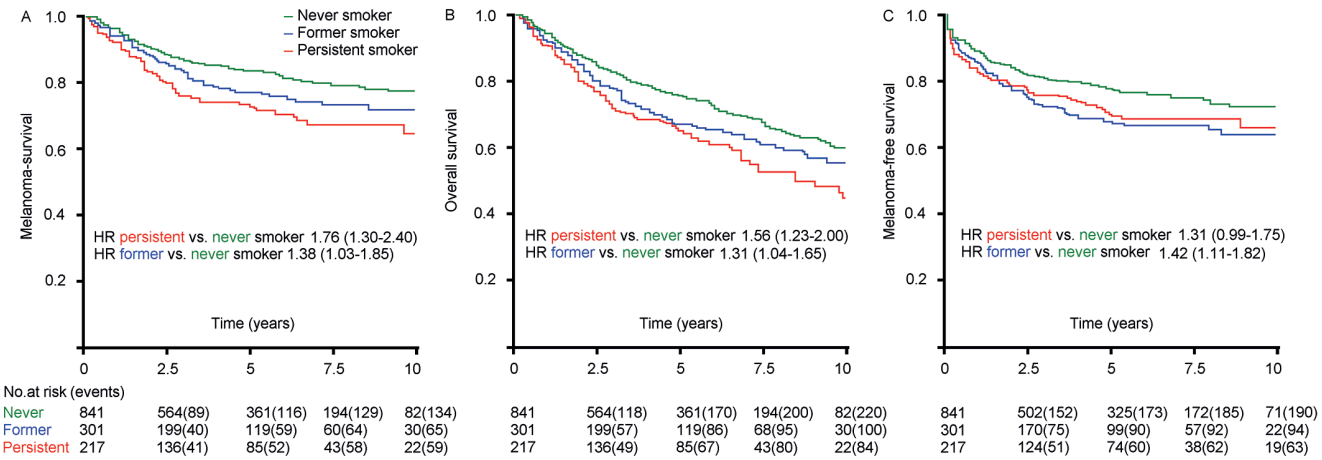

Fig. 1. Ten-year survival in melanoma patients with known smoking status. (A) Melanoma-specific survival, (B) overall survival, and (C) melanoma-free survival with unadjusted hazard ratios (HR) according to smoking status.

Table II. Multivariable Cox regression model of the adjusted risk of death from melanoma

Covariate	Hazard ratio	95% CI	*p*-value
Persistent vs never smoker	1.81	1.27–2.58	0.001
Former vs never smoker	1.75	1.28–2.40	0.001
Age over 70 years	1.57	1.21–2.04	0.001
Male sex	1.31	1.00–1.71	0.05
CCI ≥1	1.24	0.96–1.60	0.10
Stage II vs I	3.89	2.90–5.20	<0.001
Stage III vs I	8.70	6.13–12.20	<0.001
Stage IV vs I	52.6	33.33–83.33	<0.001

Complete data from 1,359 patients.
CI: confidence interval; CCI: Charlson Comorbidity Index.

were, on average, 4 years older than women (Table SI). Respectively, patients aged >70 years presented more often with stage II melanomas, had more comorbidities, lower BMI, and poorer performance status compared with younger patients (Table SI). The impact of smoking status on survival according to age is shown in Fig. S2. In the subgroup Kaplan–Meier analysis, smoking was associated with decreased MSS and OS only in patients under 70 years old (Fig. S2A, B).

Smoking impairs survival in stage IV melanoma

Kaplan–Meier subgroup analysis of MSS was performed according to smoking status and melanoma stage at melanoma diagnosis. The results are shown in Fig. S3, where significant differences in survival were seen only in patients with primary stage IV melanoma ($n=139$). Moreover, we further studied the group of patients ($n=351$) who presented with stage IV disease during the entire study period. Within stage IV melanoma patients, the median MSS was 10.4 (6.5−14.3), 14.6 (9.1−20.1), and 14.9 (11.4−18.4) months, $p=0.01$ in persistent, former, and never smokers. The median OS was 10.4 months (6.5−14.3), 13.9 (8.6−19.2), and 14.9 (11.7−18.1) months, $p=0.01$, respectively (**Fig. 2**).

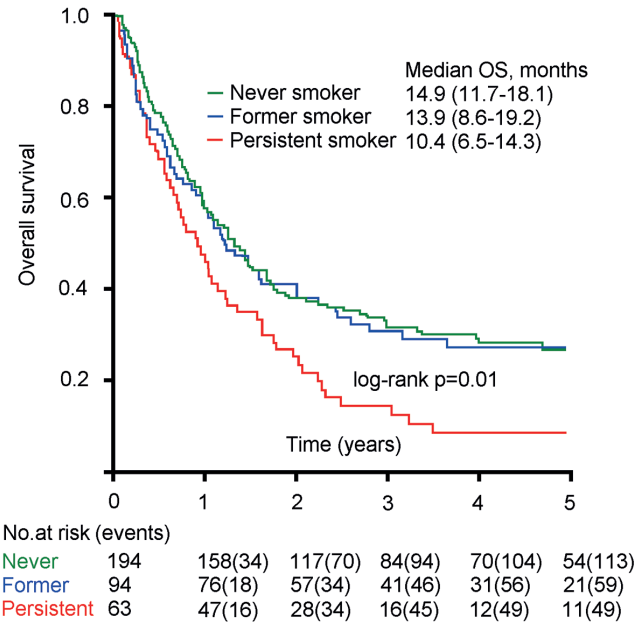

Fig. 2. Overall survival (OS) of 351 patients with stage IV melanoma according to smoking status.

DISCUSSION

Although smokers seem to have lower incidence of cutaneous melanoma (2, 6−10), several studies suggest that patients with melanoma who continue to smoke have impaired survival (17−19). Smoking has been connected to poor prognostic factors in melanoma, such as higher Breslow thickness, microscopic tumour ulceration, and sentinel lymph node metastases (22). However, conflicting results on smoking and melanoma survival are also reported (7) and the exact association between poor prognosis and smoking status is far from clear.

The current study found that smoking was an independent poor risk factor, nearly doubling the risk of death from melanoma while accounting for age, sex, TNM stage, and comorbidities in the multivariable Cox regression analysis. As expected, TNM stage (including Breslow thickness, ulceration, lymph node, and metastasis status) had the greatest impact on survival in the multivariable analysis. The negative impact of smoking on MSS and OS was most evident in stage IV patients and in younger patients (<70 years). Older patients are most likely to die from other causes than melanoma, where smoking may also play an important role. Male sex was a borderline risk factor of inferior survival in the current study cohort. These results are consistent with previous observations indicating that men and elderly patients with melanoma have inferior survival (4, 14, 15, 19). The effect of smoking on melanoma-free survival was statistically significant between never and former smokers but did not reach statistical significance between never and persistent smokers in this study cohort.

The proportion of never smokers was higher among women in the current study cohort (74% of women vs 51% of men). The metabolism of nicotine is more rapid in women than in men, possibly affecting smoking behaviour and the metabolism of tobacco-derived carcinogens (23), which may, in part, explain the shorter survival among men with melanoma. Unfortunately, we also noticed that smoking habits of patients with melanoma did not change over the period of 15 years, and smoking status was not documented into medical records for 31% of patients with melanoma treated at the study hospital. Moreover, smoking cessation year was seldom reported, making it difficult to analyse the impact of smoking cessation on subsequent survival. This underscores, that healthcare professionals should be further educated to include smoking status as a part of relevant medical history for all cancer patients including patients with melanoma.

Tobacco smoke contains over 70 known carcinogens (24) and there are numerous proposed biological mecha-

nisms explaining impaired survival in cancer patients who continue to smoke. Exposure to tobacco smoke increases proliferation, migration, invasion, metastasis, and angiogenesis of cancer cells promoting the survival and spread of cancer (25). Smoking may also alter the distribution and metabolism of several anticancer drugs by inducing the activity of cytochrome P450 (CYP) enzymes (26), and induce resistance to therapy, e.g. seen in non-small cell lung cancer patients treated with epidermal growth factor receptor tyrosine kinase inhibitors (27). In addition, smoking has numerous effects on the activity of the immune system generally, weakening immunity against infections and promoting autoimmunity (25, 28). It has been speculated that persistent smokers may derive less benefit from immune checkpoint inhibitors, although this might be outweighed by higher tumour mutational burden among smokers (29). However, results concerning smoking and BRAF and MEK inhibitors or immune checkpoint inhibitors in cutaneous melanoma could not be found, since smoking status is rarely even collected in clinical trials (30).

The limitations of the current study are attributed to the retrospective collection of study data from original medical records. There were missing information on some relevant prognostic factors, especially BRAF mutation status and ulceration. However, the distribution of BRAF mutation and ulceration was similar in persistent, former, and never smokers. The medical history of patients with melanoma did not contain comprehensive information on education, socioeconomic status, travel habits, and the use of sunbeds, limiting the opportunity to compare these results with the results of previous reports (2, 4). During 2005 to 2019, approximately half of the patients had received active systemic treatment (chemotherapy, immune checkpoint inhibitors, or BRAF and MEK inhibitors) for stage IV disease regardless of their smoking status. Chemotherapy has limited efficacy in stage IV melanoma. BRAF and MEK inhibitors and PD-1 inhibitors became available in Finland only after 2014 (31) explaining short MSS and OS in stage IV patients. Due to the relatively small number of stage IV patients (n=351) treated at single centre, we were not able to analyse the effect of smoking on different cancer treatments. However, the 3–4 months' survival benefit seen in never and former smokers compared with persistent smokers is clinically relevant in stage IV melanoma and supports advising patients to stop smoking.

In conclusion, this study shows the association of both persistent and former smoking with higher melanoma mortality in a cohort of 1,359 cutaneous melanoma patients irrespective of age, sex, stage, and comorbidities. The detrimental effect of smoking appears to be most marked in stage IV melanoma. These results emphasize the need to ask about smoking habits, and that support for patients to stop smoking should be integrated into routine care of patients with melanoma.

ACKNOWLEDGEMENTS

The study is financially supported by State Competitive Research Funds, Finnish Cancer Foundation, Juho Vainio Foundation (EH), and Eschner Foundation (PV).

The authors have no conflicts of interest to declare.

REFERENCES

1. Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. Lancet 2014; 383: 816–827.
2. Sondermeijer L, Lamboo LGE, de Waal AC, Galesloot TE, Kiemeney LALM, van Rossum M, et al. Cigarette Smoking and the risk of cutaneous melanoma: a case-control study. Dermatology 2020; 236: 228–236.
3. Pitkäniemi J, Malila N, Tanskanen T, Degerlund H, Heikkinen S, Seppä K. Cancer in Finland 2019. Cancer Society of Finland Publication No. 98, Helsinki 2021.
4. Jiang AJ, Rambhatla PV, Eide MJ. Socioeconomic and lifestyle factors and melanoma: a systematic review. Br J Dermatol 2015; 172: 885–915.
5. de Vries E, van de Poll-Franse LV, Louwman WJ, de Gruijl FR, Coebergh JW. Predictions of skin cancer incidence in the Netherlands up to 2015. Br J Dermatol 2005; 152: 481–488.
6. Dusingize JC, Olsen CM, Pandeya N, Thompson BS, Webb PM, Green AC, et al. Smoking and cutaneous melanoma: findings from the QSkin Sun and Health Cohort Study. Cancer Epidemiol Biomarkers Prev 2018; 27: 874–881.
7. Gibson J a. G, Dobbs TD, Griffiths R, Song J, Akbari A, Whitaker S, et al. The association of smoking and socioeconomic status on cutaneous melanoma: a population-based, data-linkage, case-control study. Br J Dermatol 2020; 182: 1136–1147.
8. Freedman DM, Sigurdson A, Doody MM, Rao RS, Linet MS. Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort. Cancer Causes Control 2003; 14: 847–857.
9. Odenbro A, Gillgren P, Bellocco R, Boffetta P, Håkansson N, Adami J. The risk for cutaneous malignant melanoma, melanoma in situ and intraocular malignant melanoma in relation to tobacco use and body mass index. Br J Dermatol 2007; 156: 99–105.
10. Kessides MC, Wheless L, Hoffman-Bolton J, Clipp S, Alani RM, Alberg AJ. Cigarette smoking and malignant melanoma: a case-control study. J Am Acad Dermatol 2011; 64: 84–90.
11. Mills CM, Hill SA, Marks R. Altered inflammatory responses in smokers. BMJ 1993; 307: 911.
12. Song F, Qureshi AA, Gao X, Li T, Han J. Smoking and risk of skin cancer: a prospective analysis and a meta-analysis. Int J Epidemiol 2012; 41: 1694–1705.
13. Gershenwald JE, Scolyer RA. Melanoma Staging: American Joint Committee on Cancer (AJCC) 8th Edition and Beyond. Ann Surg Oncol 2018; 25: 2105–2110.
14. Dimitriou F, Krattinger R, Ramelyte E, Barysch MJ, Micaletto S, Dummer R, et al. The World of melanoma: epidemiologic, genetic, and anatomic differences of melanoma across the Globe. Curr Oncol Rep 2018; 20: 87.
15. Lasithiotakis K, Leiter U, Meier F, Eigentler T, Metzler G, Moehrle M, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. Cancer 2008; 112: 1795–1804.
16. Chang CK, Hsieh YS, Chen PN, Chu SC, Huang JY, Wang YH, et al. A cohort study: comorbidity and stage affected the prognosis of melanoma patients in Taiwan. Front Oncol 2022; 12: 846760.
17. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. Int J Cancer 2013; 132: 401–410.
18. Wang Y, Tao H, Paxton RJ, Wang J, Mubarik S, Jia Y, et al. Post-diagnosis smoking and risk of cardiovascular, cancer, and all-cause mortality in survivors of 10 adult cancers: a prospective cohort study. Am J Cancer Res 2019; 9:

2493–2514.
19. Karlsson A, Ellonen A, Irjala H, Väliaho V, Mattila K, Nissi L, et al. Impact of deep learning-determined smoking status on mortality of cancer patients: never too late to quit. ESMO Open 2021; 6: 100175.
20. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649–655.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–383.
22. Jones MS, Jones PC, Stern SL, Elashoff D, Hoon DSB, Thompson J, et al. The Impact of smoking on sentinel node metastasis of primary cutaneous melanoma. Ann Surg Oncol 2017; 24: 2089–2094.
23. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P. Female sex and oral contraceptive use accelerate nicotine metabolism. Clin Pharmacol Ther 2006; 79: 480–488.
24. Moodie C, Best C, Critchlow N, Hitchman S, Stead M, McNeill A. The impacts of including information about the number of carcinogens in smoke on standardized cigarette packs in the UK. Eur J Public Health 2021; 31: 1031–1037.
25. Sobus SL, Warren GW. The biologic effects of cigarette smoke on cancer cells. Cancer 2014; 120: 3617–3626.
26. Petros WP, Younis IR, Ford JN, Weed SA. Effects of tobacco smoking & nicotine on cancer treatment. Pharmacotherapy 2012; 32: 920–931.
27. Zhang P, Nie X, Bie Z, Li L. Impact of heavy smoking on the benefits from first-line EGFR-TKI therapy in patients with advanced lung adenocarcinoma. Medicine (Baltimore) 2018; 97: e0006.
28. Qiu F, Liang CL, Liu H, Zeng YQ, Hou S, Huang S, et al. Impacts of cigarette smoking on immune responsiveness: Up and down or upside down? Oncotarget 2016; 8: 268–284.
29. Sillah A, Tykodi SS, Hall ET, Thompson JA, Watson NF, Lee SM, et al. Predictive lifestyle markers for efficacy of cancer immune checkpoint inhibitors: a commentary. Future Oncol 2021; 17: 363–369.
30. Peters EN, Torres E, Toll BA, Cummings KM, Gritz ER, Hyland A, et al. Tobacco assessment in actively accruing National Cancer Institute Cooperative Group Program Clinical Trials. J Clin Oncol 2012; 30: 2869–2875.
31. Mattila KE, Vihinen P, Ramadan S, Skyttä T, Tiainen L, Vuoristo MS, et al. Combination chemotherapy with temozolomide, lomustine, vincristine and interferon-alpha (TOL-IFN) plus vemurafenib or TOL-IFN as first-line treatment for patients with advanced melanoma. Acta Oncol 2020; 59: 310–314.