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Primary Lung adenocarcinoma: characteristics by gender and smoking habit

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ABSTRACT

The incidence of adenocarcinoma is increasing, particularly among women. We sought to assess the role of tobacco consumption in clinical presentation according to gender.

In this retrospective study, 848 patients diagnosed between 1997 and 2006 in Grenoble University Hospital, France, were stratified into four groups according to smoking habit. Differences between genders, and two contrasting female profiles emerged. Female current smokers were younger than never-smokers (median 51 vs 69 years, $p<10^{-3}$), more often had surgery (62.7% vs 39%, p=0.01), and had a median estimated survival of 26.2 $CI_{95\%}$[18.1-49.2] vs 15.1 months $CI_{95\%}$[12.8-22.2], p=0.002. Both groups had similar survival when taking treatment into account. Among men, smoking did not influence presentation. Male current smokers were older than female current smokers (median 59 years, $p<10^{-3}$), fewer had surgery (48.8%, p=0.015), although the percentage of stage IIIb-IV was similar (53% and 46%, pNS), and they had poorer estimated survival of 14.3 months $CI_{95\%}$[13.0-18.5] (p=0.0024). Men smoked more than women (median packs/year: 41 vs. 30, $p<10^{-3}$). Quitting smoking delayed age at diagnosis by 11 years for women (p=0.0035) and 8 years for men ($p<10^{-3}$).

Our results support the hypothesis that carcinogenesis differs between men and women, and between women smokers and never-smokers.

Keywords: Gender, Primary Lung Adenocarcinoma, Smoking, Survival

INTRODUCTION

For over 20 years, the incidence of primary lung adenocarcinoma (ADC) has been increasing [1, 2]. Squamous cell carcinomas and small cell carcinomas (SCC) are strongly linked to smoking [3,4,5] while adenocarcinoma is often found in women and never-smokers [2,5,6,7,8,9,10,11]. There are large differences across studies in the characteristics of never-smokers with non-small-cell-lung-cancer (NSCLC), including those with adenocarcinoma.
The multidisciplinary thoracic oncology meetings (MTOM), that have been held since 1976, at Grenoble University Hospital, recommend a treatment strategy including palliative care, taking into account clinical presentation and cancer characteristics.
The proportion of adenocarcinoma cases discussed in these meetings (MTOM) increased from 22.7% between 1982 and 1986 to 42.9% between 2002 and 2006. For the period between 1997 and 2006, we also observed a higher proportion of never-smokers among adenocarcinoma patients (15.3%) than among small cell and squamous cell cancer patients (2.6%, 23/885).
The aim of this study was to compare the characteristics and outcomes of patients with adenocarcinoma, between smokers and never-smokers according to gender.

METHODS

Population

This is an observational single-centre study from the multidisciplinary thoracic oncology meetings of Grenoble University Hospital, France, a regional teaching hospital. All patients discussed at the MTOM presenting with adenocarcinoma between 1997 and 2006 were included.

Data collected

Data were collected prospectively and recorded in the MTOM database. Information included age at first treatment, gender, characteristics of the tumour site (CIMO), cTNM and pTNM (UICC 1987-98 and 2003), histological type (WHO SNOMED classification), WHO performance status (PS), tobacco consumption with the number of packs by years (PY), number of years since quitting, date of first treatment, loco-regional recurrence, first metastasis and latest follow-up, vital status of patient and, in case of death, date and cause. Data were extracted from the database on February 15, 2010 and vital status was also updated at this time. Patient outcomes were obtained from hospital records, well-established contacts with primary care physicians and municipal registries of deaths.

For never-smokers, any occupational exposure was identified through collaboration with the Department of Occupational Disease. The data from our hospital records were compared with data from the Isère Cancer Registry (County Epidemiological Register for Cancer).

Patients were assigned to one of four groups according to their smoking habits at the date of treatment initiation [11].

1. Never-smokers : less than 100 cigarettes in their whole life (NS)
2. Current smokers: Patients still smoking or having quit within the past year (CS)
3. Former smokers: Patients having quit more than 1 year ago (FS)
4. Undefined smokers: current or former smokers where information on quitting was unavailable (US). This group (4 women and 22 men) is not specifically described here, but was included in the "Smokers" group for statistics and survival curves.

For the relevance of some results, patients with a history of smoking (CS + FS + US) were grouped into a cohort called "Smokers" (S).

Statistical Analysis

Only variables for which data were complete for over 80% of cases were used.

The clinical characteristics of the different study groups were compared using Chi^2 or Fisher

tests and means were compared using Student's t-test. Median duration of follow-up was calculated using the inverted Kaplan Meier method. The start date for survival was the date of first treatment.

The clinical variables suspected to be associated with survival were tested in univariate analysis using the nonparametric Log Rank test. Variables (except smoking related ones) with $p<0.2$ in the univariate analysis were subjected to a stepwise selection procedure for a multivariate Cox model (overall survival) or Fine and Gray model (lung cancer-specific survival). Variables with $p<0.05$ in the multivariate analysis were retained in the model. Since the risk of death from lung cancer and death from another cause compete, the Cox model was not suitable for assessing lung cancer-specific survival (violation of uninformative censoring assumption). We therefore used the Fine and Gray model, which is an adaption of the Cox model that overcomes the uninformative censoring problem. The effect of smoking was tested by forcing the variable in the multivariate prognostic models (overall death and lung cancer-related death). P values <0.05 were considered significant. All statistical analyses were performed using SAS 9.13 (Cary, NC).

RESULTS

We identified 984 adenocarcinomas and the study analysis concerned the 848 cases with documented smoking status, including 225 women (26.5%). Adenocarcinoma cases with missing smoking status were equally distributed by gender ($p = 0.51$). A comparison of our hospital data with the Isère Cancer Registry over a similar period showed no difference between the two populations concerning sex, median age at first treatment and histological type (eTable 1).

Exhaustivity

We estimate that approximately 87 % $CI_{95\%}$ [71.0-96.5%] of all types of lung cancer registered in the hospital database are discussed at the MTOM. Of NSCLC patients reviewed in the study period 12.1% were recommended to receive palliative care only.

Age at first treatment (Table 1)

The median age at first treatment was 61 years, with no significant differences between men and women. However age at first treatment in women "Smokers" was lower than in men, respectively 52 years versus 62 years ($p \leq 0.001$). In contrast, among the NS group, women were 8 years older than men ($p = 0.037$). For men no difference in age was found between the different smoking groups. However, female current smokers were 18 years younger than female never-smokers ($p \leq 0.001$). (eFig 1 and 2)

Quitting smoking delayed the median age of diagnosis by 8 years for men and 11 years for women, in comparison with active smokers.

There was a higher percentage (23%) of women in the 'under 50' group and among them 86.5% were smokers and 73% still smoked (Table 2). Their smoking profile was similar to that of men in the same age group. In contrast, men diagnosed before age 50 made up only 11.7% of all men in the study population ($p \leq 0.001$).

In women the proportion of never-smokers increased significantly with age from 13.5% under age 50 to 74.1% over age 70. However, in men, this proportion did not vary with age, with an overall percentage of 4.8%. (eFig 3)

Diagnosis of adenocarcinoma in never-smokers before 50 years of age was rare (1.4% of cases), but with a significant difference between men (5/623) and women (7/225) ($p = 0.02$) (Table 2).

Occupational Exposure

To try to explain age differences between male never-smokers and female never-smokers we analysed data on occupational exposure in these groups (respectively n=25 and n=81 cases documented). Taking all types of exposure together, men underwent greater exposure (44%) than women (13.6%; $p \leq 0.001$). In particular, men were more frequently exposed to asbestos (24%) than women (3.7%; $p = 0.005$).

Tobacco consumption

Distribution by smoking status is given in Table 2. Never-smokers represented 15.3% of patients, of whom 77% were women. While nearly half the women were never-smokers (44.4%), only 4.8% of men had never smoked.

In current smokers, tobacco consumption was higher in men, median 50 PY $CI_{95\%}$ [46.7-53.3], compared with women, 35 PY $CI_{95\%}$ [29.9-40.1] ($p \leq 0.001$). The same was true for the smokers group, with a median of 41 PY $CI_{95\%}$ [38.3-43.7] for men vs. 30 PY for women $CI_{95\%}$ [25.3-34.6] ($p \leq 0.001$). Age at first treatment was found to be directly related to extent of tobacco consumption (Fig. 1) for both sexes.

Disease Severity

Disease severity varied according to gender and smoking habit (Table 2). In women, never-smokers more often presented clinical stages IIIb and IV than current smokers ($p = 0.01$) or smokers ($p = 0.03$) and they were less frequently treated by surgery. These differences were not significant between male groups. Male current smokers underwent surgery less often than women current smokers ($p = 0.015$).

Women had a better performance status than men ($p \leq 0.001$), and in particular, female never-smokers had better PS than male never-smokers ($p = 0.007$) (Table 2).

Trends over time

During the study period, the percentage of women diagnosed increased steadily, from 17.6% in 1997 to 31.1% in 2006. The proportion of female never-smokers decreased (eFig.4.).

Survival

Survival results are shown in Table 3. Fourteen patients (1.6%) were lost to follow-up. The median follow-up was 50 months, $CI_{95\%}$ [46-55]. Of the women 160/225 had died (71%) including 66.4% in the smokers group and 77% of never-smokers. A slightly higher proportion of men had died (495/623, 79.5%), including 79.2% of smokers and 83% of never-smokers. Among the patients who died, 88.2% died from lung cancer (eTable 2).

Female never-smokers, often older and with less surgery, had a poorer prognosis than female smokers ($p = 0.028$) or current smokers ($p = 0.002$). However, this difference disappeared when adjusting for therapeutic options (Table 3, Figures 2 and 3).

Significant differences in survival included longer survival for women versus men in both the smokers and current smokers groups ($p = 0.002$, $p = 0.0024$ respectively).

In univariate analysis (Table 4), factors reducing overall survival included older age, male, PS >1, clinical stage >IIIa, no surgery, and the year of treatment. The improved prognosis after 2004 might reflect the emergence of targeted therapies. Smoking status, extent of consumption and quitting smoking did not influence survival.

In multivariate analysis (Table 5), the unfavourable prognostic factors were age >70 years, male gender, PS >1, advanced clinical stage and no surgery. Smoking status did not influence survival (eTable 3).

Analysis of specific deaths from cancer revealed the same risk factors in the univariate analysis (eTable 4). However, in multivariate analysis, gender did not influence specific survival and current smoking seemed to be a pejorative factor in both sexes (eTable 5).

DISCUSSION

Taking our results together, for women we propose two contrasting patient profiles:

1) Female never-smoker: older, with few symptoms, diagnosed late. Median survival is comparable to male never-smokers but worse than that of young women smokers, although an analysis of survival according to surgery showed no significant difference.

2) Female current smoker: young, smokes less than male current smokers, in good physical condition. Surgery is more frequently feasible, with longer survival than the other groups, although 5-year survival remains poor. Without surgery, the prognosis is highly pejorative and comparable to that of the much older female never smokers.

For men, no specific profile in terms of smoking, age, PS, extent of tumour and survival could be proposed.

Our study confirms that adenocarcinoma is linked to smoking in men, but much less so in women. We found that a large number of never-smokers with adenocarcinoma were women (77%), in line with findings in the literature [2,5,6,8,9,11,12,13,14,15,16].

Women who smoke are more often younger than men [9,10] with the average age difference being usually from 3 to 6 years. An excess of women under 50 has also been noted by Radzikowska et al [10] and in our study 86.5% of this group were smokers.

For carriers of either adenocarcinoma or NSCLC a median age ranging from 63.5 to 70 years is found in the literature for never-smokers [8,17], and a more advanced age for women never-smokers (2, 13). However, the existence of two distinct generations of women presenting with adenocarcinoma depending on smoking status, has not previously been found and is particular to our study. This might be linked to later and less frequent smoking in women in Europe and in our region of France than in the US. The younger female smokers in our study were born between 1947 and 1956. They were teenagers or young adults in 1968 and represent the first generation to be influenced by more permissive attitudes towards

smoking by women. In contrast, only Asian studies reveal adenocarcinoma patients in non-smoking groups to be younger than those in smoker groups [6,18].

We found that the proportion of female patients presenting with adenocarcinoma increased over time, reaching 31.1% in 2006. The National Cancer Data Base (USA) reported for the year 2001 48% of women among patients presenting with adenocarcinoma and broncho-alveolar cancers [12]. According to Asian studies performed between 1999 and 2005, this proportion varies from 8.4% to 52.5% [3,9]. These differences may reflect very different habits, exposure, and genetic and environmental factors between populations.

Our study confirms that women smoke less than men [2,7,19] and supports the suggestion that they are more susceptible to carcinogens in cigarette smoke [16]. However we have no information on passive smoking in never-smoking patients, a recognized a risk factor [2,14,15,19,20,21,22], particularly in certain ethnic subgroups (e.g. Asian women) [17].

We confirm the beneficial effect of quitting smoking in both sexes, which can delay the age of onset by almost ten years. We found no improved survival for the former-smokers group, even among those having quit smoking for more than 12 years, but this group covers many different patterns of tobacco consumption. Women have a better performance status than men [7], as confirmed here, which is attributed to an excess of co-morbidities in men related to alcohol, greater occupational exposure and heavier smoking. The good PS found in women never-smokers can be explained by fewer respiratory and cardiac co-morbidities. At presentation for adenocarcinoma they were older, with more advanced clinical stages, suggesting a delay in diagnosis in this group, longer latency of the disease and/or a slower progression of the disease than in women who smoke. Also, the lack of respiratory and cardiac co-morbidities, the good PS and no tobacco exposure means that the primary care physician's attention is not drawn to the possibility of lung cancer.

Several authors have reported the advanced stage at diagnosis among female never-smokers,

with 62.5% to 71% having stage IIIb-IV tumours [8,14] in studies that focus on NSCLC. At this late stage, recourse to surgery is limited for these female never-smokers and is the main handicap to their survival.

In the NS group, in agreement with the literature, we confirm the prevalence of occupational exposure in men [2,14,16,22]. This could explain the younger median age at diagnosis, by 8 years, for men compared with women.

Ultimately, the large proportion of female never-smokers and the earlier age of onset of adenocarcinoma in women who do smoke, albeit less than men, suggest an increased susceptibility in women. In the literature, we find this notion of "greater susceptibility" among women, who accumulate multiple deficits: reduced clearance of nicotinic derivatives, poorer ability to repair DNA, an activating role of certain hormones such as gastrin-releasing peptide and estrogens, all of which may contribute to "accelerated" carcinogenesis [2,15,16,22,23]. This could explain the poorer survival of women smokers, particularly when surgery is no longer feasible (Figure 3), supporting the hypothesis of a more aggressive tumour.

Differences in clinical presentation support the hypothesis that carcinogenesis differs between smokers and never-smokers [2,11,14,24] and between men and women [2,5,16,25], as evidenced by the greater proportion of EGFR mutations, with greater sensibility to tyrosine kinase inhibitors in female never-smokers. However, some authors dispute such differences [26].

Men with adenocarcinoma have been found to have a history of tobacco consumption similar to that for other histological types of tumour, such as squamous and SCC. The tendency towards adenocarcinoma might be explained by the composition of cigarette smoke [2].

For equivalent levels of smoking, women have a better prognosis than men. This observation is found in numerous studies with uni- or multivariate analysis for NSCLC or adenocarcinoma alone [7,9,10,16,25].

We found that neither overall survival nor lung cancer survival to be significantly influenced by smoking in either the uni- or multivariate analysis for either sex. In contrast to observations in some cohorts [9,11,14,17,18], the prognosis for never-smokers was no better than for smokers. The younger age of female smokers and earlier diagnosis made surgical intervention more feasible, explaining their better survival than female never-smokers. Nevertheless, their prognosis remained poor, with low rates of 5-year survival. The message of prevention by abstaining from smoking is still highly relevant, especially as young female smokers presenting at an inoperable stage have catastrophic survival. Other authors found similar survival for NSCLC in smokers and never-smokers [6,8] but without any distinction by sex. The excess of deaths in NS men compared with NS women is also controversial. [26,27].

Survival and presentation of adenocarcinoma as a function of smoking varies between studies and differences may be explained by the heterogeneity in the populations analysed and in the comparisons made.

Our study has several limitations. This was a single centre retrospective observational study conducted at a large regional university hospital. However, on the basis of comparisons made with the cancer registry data, we believe that the study population is representative of our region. We were not able to discuss all of the lung cancer cases presenting at the hospital. However the vast majority of these cases were included in the study. The missing cases were mainly patients with very poor prognosis with no therapeutic outcome. A potential bias is the underestimation of pack.years for smokers because of the possible subjectivity of this information, which was collected during the initial and subsequent medical consultations.

CONCLUSION

We confirm the disturbing susceptibility of women to adenocarcinoma. The study highlights major differences in presentation between women according to smoking status, leading to the existence of different "generations" of female patients.

For female never-smokers, we hypothesize a disease with extended latency, explaining the often pejorative presentation, relatively late diagnosis, and poor prognosis, although the advent of targeted therapies and earlier diagnosis may change this outcome.

In contrast, young women smokers who smoke less than men and for whom surgery is not feasible have a very poor survival rate. This argues for a particularly aggressive form of the disease, greater susceptibility and accelerated carcinogenesis.

Differences in clinical presentation between women smokers and never-smokers and the absence of specificity in men raise the question as to whether there are differences in carcinogenesis between men and women and between women smokers and never-smokers. Variations in mutational profile between smokers and never-smokers might provide the beginning of an explanation [11,18,24] and give hope for a better therapeutic response to targeted therapies (the Interest study) [28]. Diagnostic innovations such as the development of a tumour identity card could facilitate these tailored therapeutic applications [29, 30].

These results provide an incentive to improve preventive measures targeted at women and to alert primary care physicians to the risks of adenocarcinoma in female never-smokers.

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TABLES

Table 1. Age at first treatment

	Total	Current smokers	Former smokers	Smokers*	Never-smokers
Men	**623**	**375**	**196**	**593**	**30**
Median age at diagnosis (years)	62	59	67	62	61
[CI 95%]	[61.0-63.0]	[57.7-60.3]	[65.3-68.6]	[61.0-63.0]	[55.9-66.1]
Min-Max	33-90	35-90	36-83	35-90	33-78
Women	**225**	**94**	**27**	**125**	**100**
Median age at diagnosis (years)	60	51	62	52	69
[CI 95%]	[57.9-62.1]	[48.2-53.8]	[56.2-67.8]	[49.4-54.6]	[66.3-71.7]
Min-Max	34-86	34-86	42-86	34-86	41-86
Total:	**848**	**469**	**223**	**718**	**130**
Median age at diagnosis (years)	61	58	66	61	68
[CI 95%]	[60.0-61.9]	[56.8-59.2]	[64.4-67.6]	[60.0-61.9]	[66.0-71.0]
Min-Max	33-90	34-90	36-86	34-90	33-86

* Smokers = current smokers + former smokers + undefined smokers

Abbreviations: CI 95% - 95% Confidence interval

Table 2. Patients' characteristics

	Total		Current smokers		Former smokers		Smokers*		Never-smokers	
	N	%	N	%	N	%	N	%	N	%
Men	**623**		**375**	***60.2***	**196**	***31.5***	**593**	***95.2***	**30**	***4.8***
<50 years	73	***11.7***	57	***15.2***	9	***4.6***	68	***11.5***	5	***16.7***
50-70 years	411	***66.0***	256	***68.3***	127	***64.8***	393	***66.3***	18	***60.0***
>70 years	139	***22.3***	62	***16.5***	60	***30.6***	132	***22.3***	7	***23.3***
Stages I to IIIA	300**	***48.5***	175**	***47.0***	103**	***53.1***	287**	***48.8***	13	***43.3***
Stages IIIb and IV	318**	***51.5***	197**	***53.0***	91**	***46.9***	301**	***51.2***	17	***56.7***
Tumour excision	320	***51.4***	183	***48.8***	116	***59.2***	308	***51.9***	12	***40.0***
PS 0-1	335**	***53.9***	195**	***52.1***	111**	***56.9***	321**	***54.3***	14	***46.7***
Women	**225**		**94**	***41.8***	**27**	***12.0***	**125**	***55.5***	**100**	***44.4***
<50 years	52	***23.1***	38	***40.4***	5	***18.5***	45	***36.0***	7	***7.0***
50-70 years	115	***51.1***	48	***51.0***	15	***55.6***	65	***52.0***	50	***50.0***
>70 years	58	***25.8***	8	***8.5***	7	***25.9***	15	***12.0***	43	***43.0***
Stages I to IIIA	98**	***43.7***	50**	***53.7***	11	***40.7***	62	***50.0***	36	***36.0***
Stages IIIb and IV	126**	***56.2***	43**	***46.2***	16	***59.3***	62**	***50.0***	64	***64.0***
Tumour excision	113	***50.2***	59	***62.7***	13	***48.1***	74	***59.2***	39	***39.0***
PS 0-1	150**	***67.0***	58	***61.7***	17**	***65.4***	77**	***62.1***	73	***73.0***
Total	**848**		**469**	***55.3***	**223**	***26.3***	**718**	***84.7***	**130**	***15.3***
Ratio M/F	73.5/26.5		80/20		88/12		82.5/17.5		23/77	

* Smokers = current smokers + former smokers + undefined smokers

** Between one and five missing values in these table cells

Abbreviations PS: WHO performance status

Table 3. Survival according to gender and cigarette smoking.

Adenocarcinoma	n	Median (months)	[IC_{95}%]	Alive at 3 years N	(%)	Alive at 5 years N	(%)
Men							
Current smokers	375	14.3	13-18.5	119	(31.7)	93	(24.8)
Former smokers	196	18.1	13.8-21.4	62	(31.6)	50	(25.5)
Never-smokers	30	19.5	14-23.7	8	(26.7)	5	(16.7)
Smokers	593	15.6	13.7-18.6	187	(31.5)	146	(24.6)
Women							
Current smokers	94	26.2	18.1-49.2	42	(44.7)	37	(39.4)
Former smokers	27	17.3	9.6-70.3	12	(44.4)	11	(40.7)
Never-smokers	100	15.1	12.8-22.2	34	(34.0)	27	(27.0)
Smokers	125	23.1	17.3-42.5	55	(44.0)	48	(38.4)
Women, treatments and smoking							
Smokers with surgery	74	68.3	49.2 – NA	51	(68.9)	45	(60.8)
Never-smokers with surgery	39	63.1	28.4 – NA	24	(61.5)	22	(56.4)
Smokers without surgery	51	9.1	4.8 – 11.4	4	(7.9)	3	(5.9)
Never-smokers without surgery	61	11.3	7.4 – 13.7	10	(16.4)	5	(8.2)
Men and Women							
Current smokers	469	16.9	13.9-20.4	161	(34.3)	130	(27.7)
Former smokers	223	18.1	13.9-21.4	74	(33.2)	61	(27.4)
Never-smokers	130	16.8	13.8-22.2	42	(32.3)	32	(24.6)
Smokers	718	17.3	14.5-19.2	242	(33.7)	194	(27.0)

(*) Kaplan Meier estimate
Abbreviations: CI 95% - 95% Confidence interval

Table 4. Univariate risk factors for Death from lung cancer

Variable	items	Alive (n=266)		Died from Cancer (n=582)		Median Survival (95% CI)	P$
(missing)		n	%	n	%		
Sex	F	78	34.7	147	65.3	22.3 (17.6 – 31.3)	0.19
	M	188	30.2	435	69.8	19.4 (16.8 – 22.5)	
Age	<50	41	29.3	99	70.7	17.2 (12.6 – 26.7)	**0.02**
	[50;60[	88	34.8	165	65.2	23.1 (18.7 – 31.4)	
	[60;70[	81	33.2	163	66.8	23.7 (20.2 – 30.6)	
	≥ 70	56	26.5	155	73.5	13.8 (12.8 – 18.8)	
PS (3)	0	25	56.8	19	43.2	87.1 (42.5 – Inf)	**<0.0001**
	1	170	38.5	271	61.5	33.8 (26.7 – 39.5)	
	≥ 2	68	18.9	292	81.1	10.7 (8.7 – 13.3)	
Tumour excision	No	47	11.3	368	88.7	8.7 (7.8 – 9.8)	**<0.0001**
	Yes	219	50.6	214	49.4	68.1 (45.6 – 92.6)	
Year of treatment	≤ 2001	90	25.3	266	74.7	17.6 (14.0 – 21.0)	**0.005**
	> 2001	176	35.8	316	64.2	22.4 (19.0 – 27.2)	
Year of treatment	≤ 2004	172	27.2	461	72.8	18.6 (15.6 – 21.0)	**0.001**
	> 2004 (Targeted Therapy)	94	43.7	121	56.3	28.9 (21.2 – 38.9)	
Clinical Stage (6)	IA	92	69.7	40	30.3	Inf	**<0.0001**
	IB	69	50	69	50	59.4 (43.3 – Inf)	
	IIA/IIB	17	34.7	32	65.3	33.8 (22.4 – 56.2)	
	IIIA/IIIB	56	26.3	157	73.7	16.0 (13.2 – 20.4)	
	IV	30	9.7	280	90.3	8.0 (6.9 – 9.6)	
Smoking	Never-smoker	35	26.9	95	73.1	18.8 (14.6 – 22.4)	0.3
	Smoker	231	32.2	487	67.8	20.7 (18.1 – 24.7)	
Smoking	Current smoker	148	31.6	321	68.4	20.4 (16.3 – 24.5)	0.2
	Undefined smoker	4	15.4	22	84.6	18.4 (11.2 – 31.5)	
	Former smoker	79	35.4	144	64.6	22.5 (17.8 – 32.0)	
	Never-smoker	35	26.9	95	73.1	18.8 (14.6 – 22.4)	
PY (103)	<20	57	31.1	126	68.9	21.0 (17.2 – 26.8)	1.0
	[20;40[	60	32.3	126	67.7	20.9 (15.7 – 31.4)	
	[40;50[	44	34.9	82	65.1	19.0 (14.1 – 33.4)	
	≥ 50	77	30.8	173	69.2	21.4 (18.5 – 25.8)	
Stopped smoking (68)	Never-smokers	35	26.9	95	73.1	18.8 (14.6 – 22.4)	0.5
	Quit ≤ 12 years	183	32.3	383	67.7	20.9 (17.6 – 24.9)	
	Quit > 12 years	27	32.1	57	67.9	20.4 (13.8 – 32.0)	

$ Fine and Gray Model; N.B.: the medians for survival are artificially increased in censured patients so as to avoid the bias of "informed censure" for patients who died from other causes.
Abbreviations PS – WHO performance status, CI - Confidence interval

Table 5. Multivariate clinical model for death (n=787)

Parameter	Modality	HR	95% CI		P$
Sex	M	1			0.01
	F	0.79	0.66	0.95	
Age	≥ 70	1.97	1.54	2.53	<0.0001
	[60;70[	1.24	0.97	1.59	
	[50;60[	1.07	0.83	1.36	
	< 50	1			
PS	2,3,4	1.60	1.35	1.89	<0.0001
	0,1	1			
Tumour excision		0.41	0.33	0.50	<0.0001
Clinical Stage	IV	2.70	2.10	3.48	<0.0001
	IIIA/IIIB	1.93	1.52	2.45	
	IIA/IIB	1.37	0.95	1.97	
	IA/IB	1			

Figure Titles and Legends

Figure 1. Relation between mean packs.year and age at diagnosis.

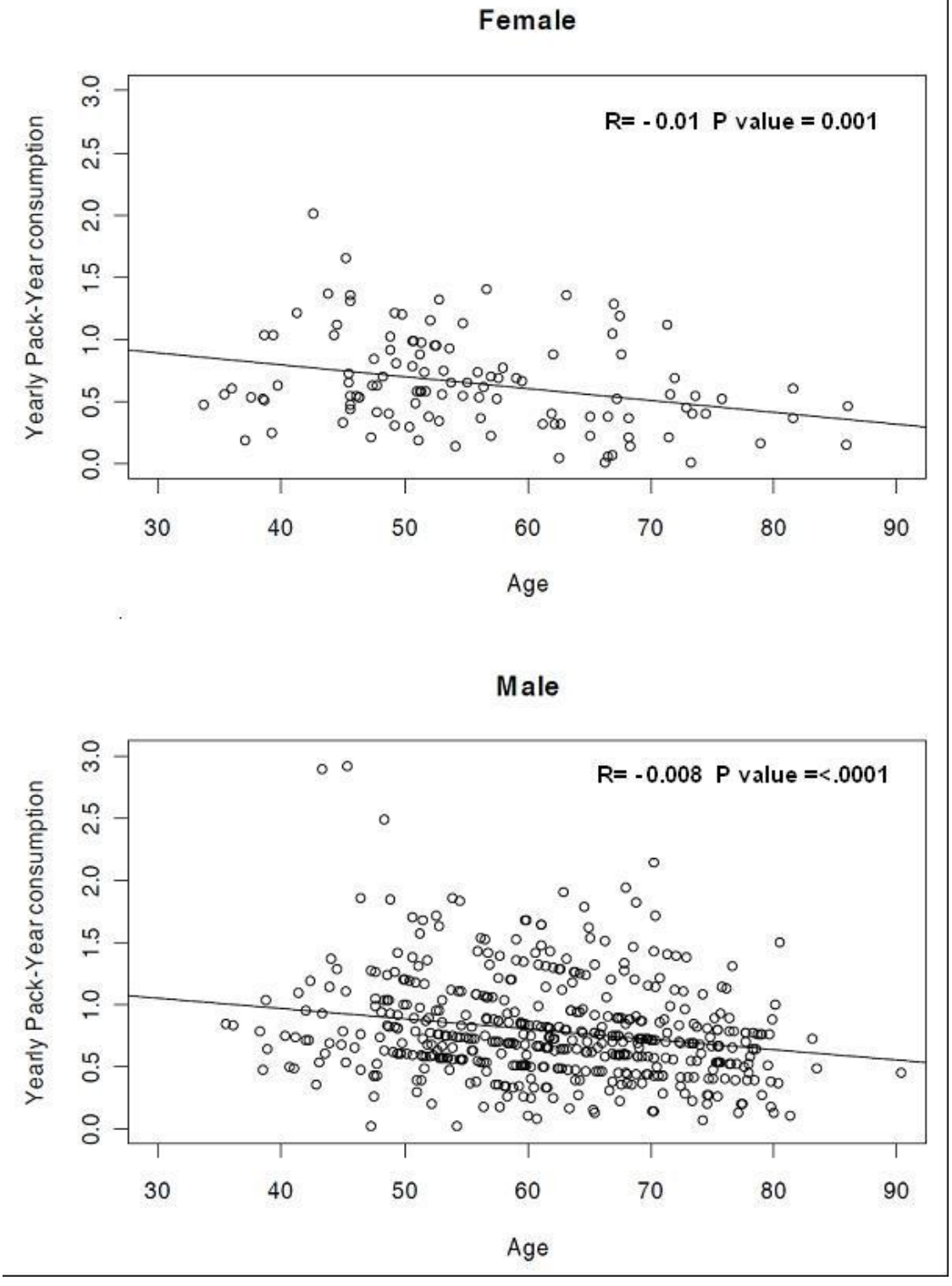
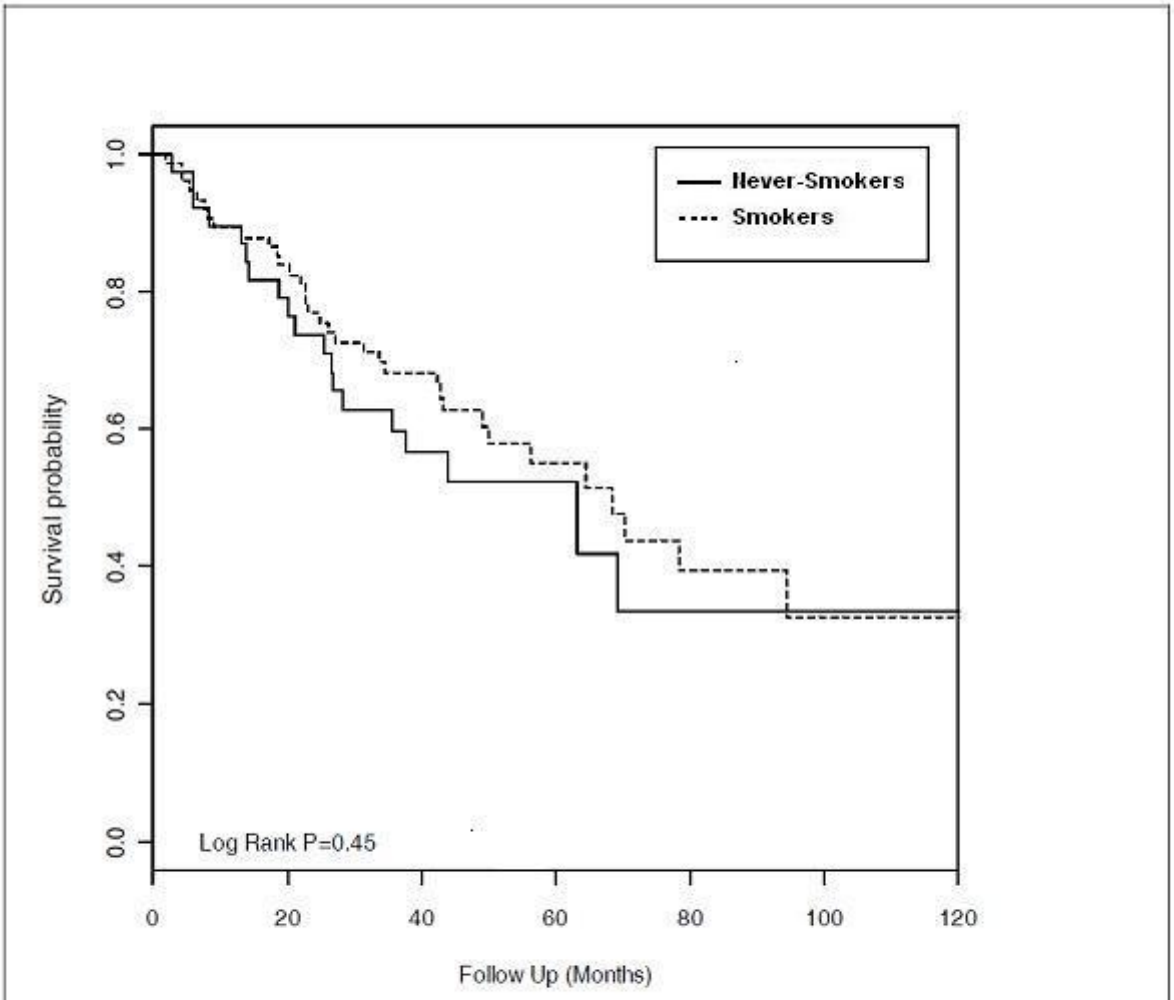
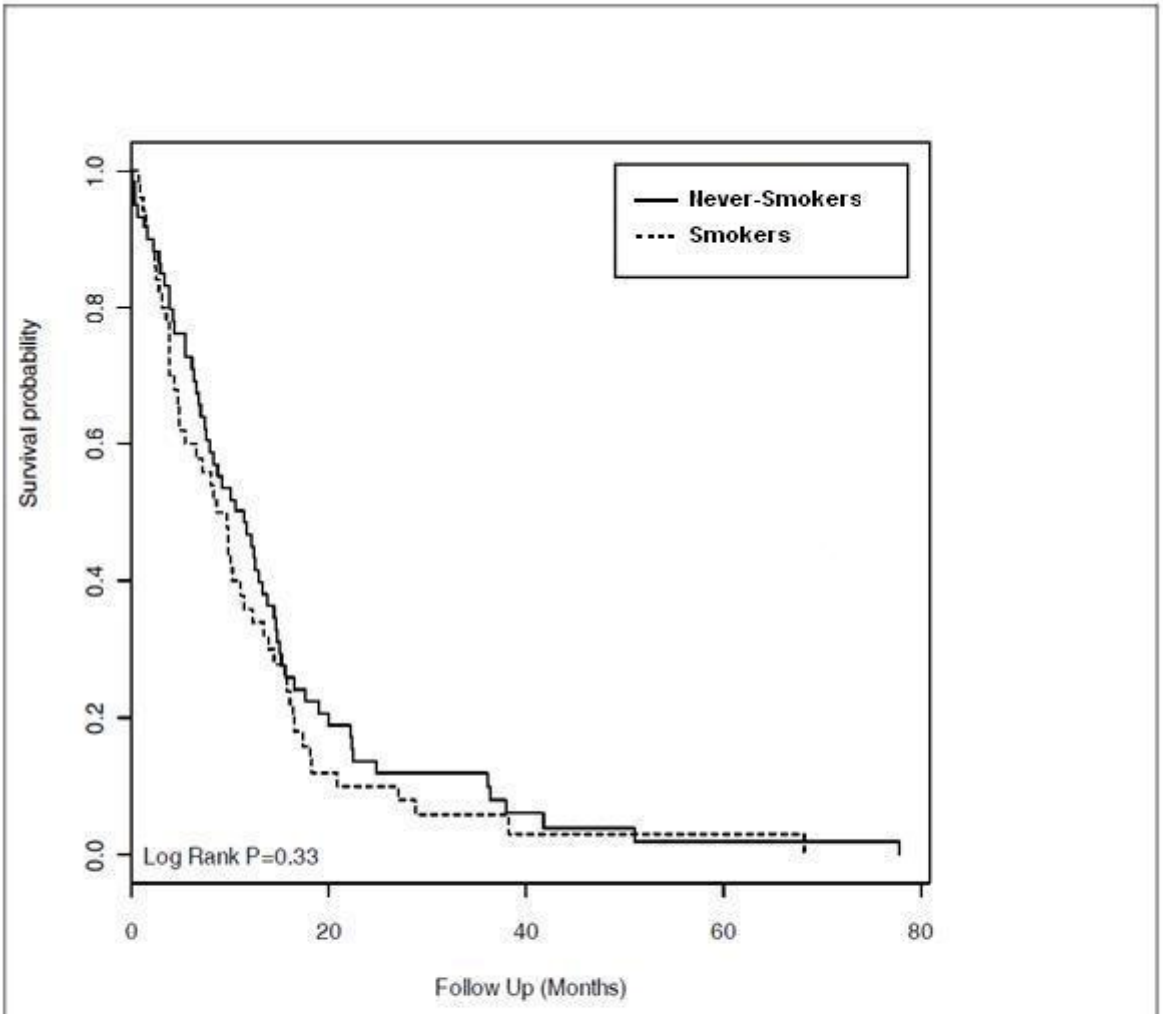


Figure 2: Survival by smoking habit for women with surgery



	Number of Subjects	Events	Truncated	Median Survival CI 95%
Smokers	74	46% (34)	54% (40)	68.3 [49.2 - NA]
Never-Smokers	39	51% (20)	49% (19)	63.1 [28.4 - NA]

Figure 3: Survival by smoking habit for women without surgery



	Number of Subjects	Events	Truncated	Median Survival CI 95%
Smokers	51	96% (49)	4% (2)	9.1 [4.8 - 11.4]
Never-Smokers	61	93% (57)	7% (4)	11.3 [7.4 - 13.7]