Impact of smoking cessation on lung cancer mortality

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Ontario Health

I have no conflicts of interest

Lung cancer risk factors

- Cigarette smoking is the main cause of lung cancer in Canada
- Tobacco smoke is a toxic mix of 7,000 chemicals; at least 70 known carcinogens
- 80-90% of lung cancer deaths due to smoking
- Other causes of lung cancer:

    radon, asbestos, arsenic, arsenic, diesel exhaust, chromium, some forms of silica

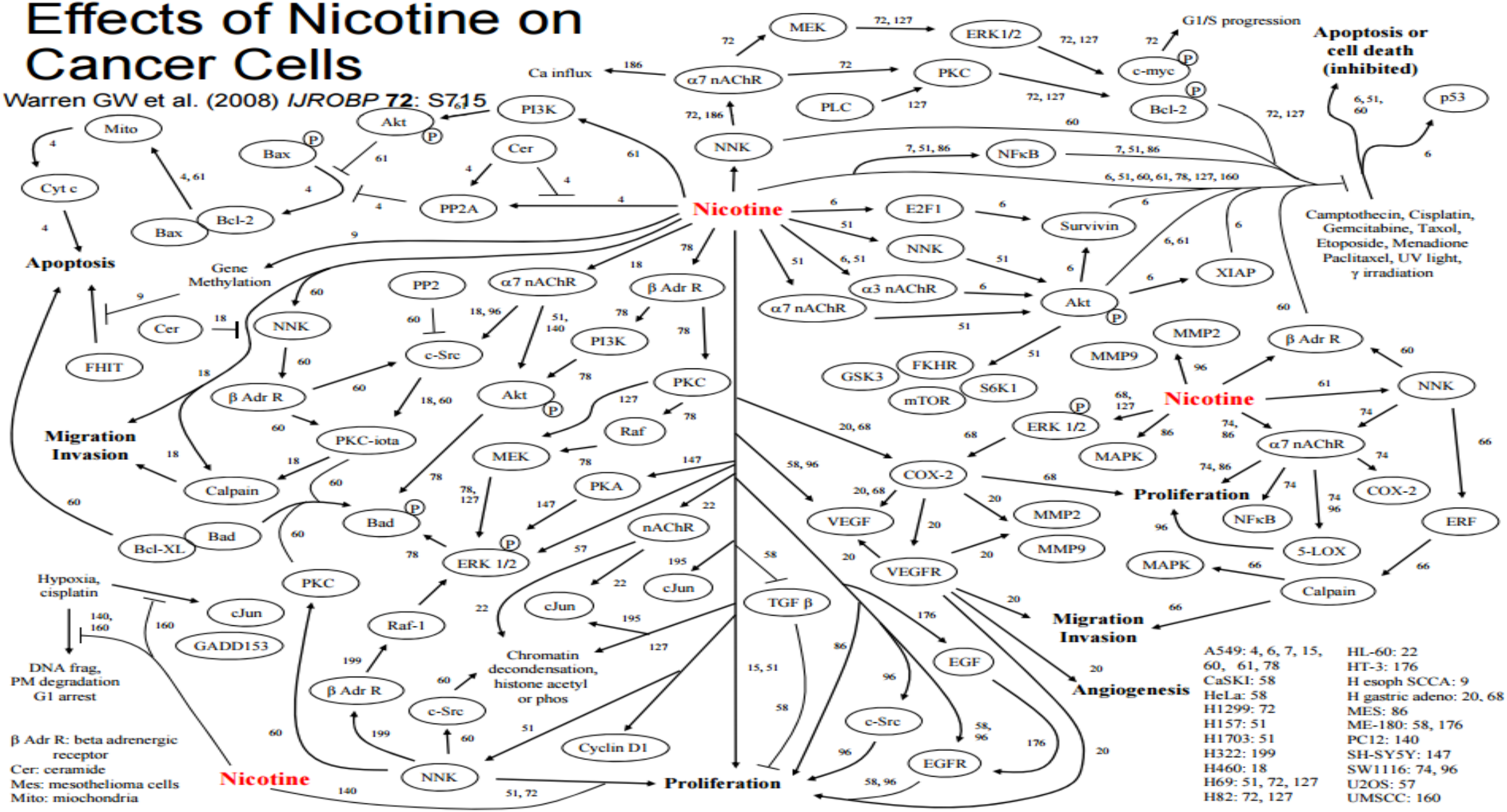
How smoking tobacco causes lung cancer

Multifactorial:

- **Carcinogens** in tobacco smoke damage lung cells leading to mutations and development of cancerous cells
- Smoking generates **free radicals** which can cause oxidative stress, cellular damage and **chronic inflammation**; continual repair process can increase risk of cancerous changes in cells
- **Weakened immune system** from smoking makes it less effective at detecting and removing cancer cells
- **Nicotine** can promote growth of tumours

Effects of Nicotine on Cancer Cells

Warren GW et al. (2008) *IJROBP* **72**: S715



Negative effects of smoking on lung cancer treatments

- Surgery: post-op complications; wound infections, dehiscence/hernia
- Radiotherapy: esophagitis, pneumonitis/fibrosis, survival (SBRT shorter 2 yr survival)
- Molecular targeted therapies, chemotherapy
- Immunotherapy

Smoking induces drug metabolizing hepatic enzymes

Drug	Enzymes	Drug Target	Adverse Reactions
Erlotinib	CYP3A4, CYP1A2, CYP1A1	EGFR	Rash Diarrhea DILI, ILD
Gefitinib	CYP3A4, CYP1A2 CYP1A1	EGFR	As above
Gemcitabine	Cytidine deaminase	Cytidine analogue	Neutropenia
Docetaxel	CYP3A4	Antimitotic	Neutropenia, anemia, thrombocytopenia, alopecia
Paclitaxel	CYP3A4, CYP2C8	Antimitotic	As above
Irinotecan	UGT1A1, CYP2C8	Topo-1 inhibitor	Neutropenia, leukopenia, diarrhea

Adapted from O'Malley MO et al JTO 2014; 9(7):917

Immunotherapy

Three recent meta-analysis examined the effect of smoking on immune checkpoint inhibitors in metastatic non-small cell lung cancer

Most recent (Dai L et al 2021) included 28 articles from 24 phase II and III randomized trials; 13,918 eligible patients

- ICIs significantly prolonged OS more than chemo in smokers (HR = 0.75, CI 0.69 – 0.81) but not in never smokers
- Subgroup analysis: ICI monotherapy significantly improved OS in smokers versus never smokers

Interpretation:

- Either ICI monotherapy or combination chemo- ICI therapy appear superior to chemo in smokers.
- ICI monotherapy and dual ICIs appear less effective in never smokers and ICIs plus chemo might be the optimal selection in these patients

Dai L et al. EClinical Medicine2021; 38:100990

Smoking cessation leads to longer survival and delayed disease progression

- 517 patients: 297 continued to smoke; 229 quit smoking:
  - The adjusted median overall survival time was **21.6 months greater** among patients who quit vs. those who continued to smoke (6.6 years vs. 4.8 years)
  - Quitting smoking was associated with longer progression-free survival (5.7 years for those who quit vs. 3.9 years for patients who did not)

Sheikh M, et al. Postdiagnosis smoking cessation and reduced risk for lung cancer progression and mortality : A prospective cohort study. Ann Intern Med. 2021 Sep;174(9):1232-1239.

Quitting smoking improves two-year survival after diagnosis of NSCLC

UK multi-centre observational study:

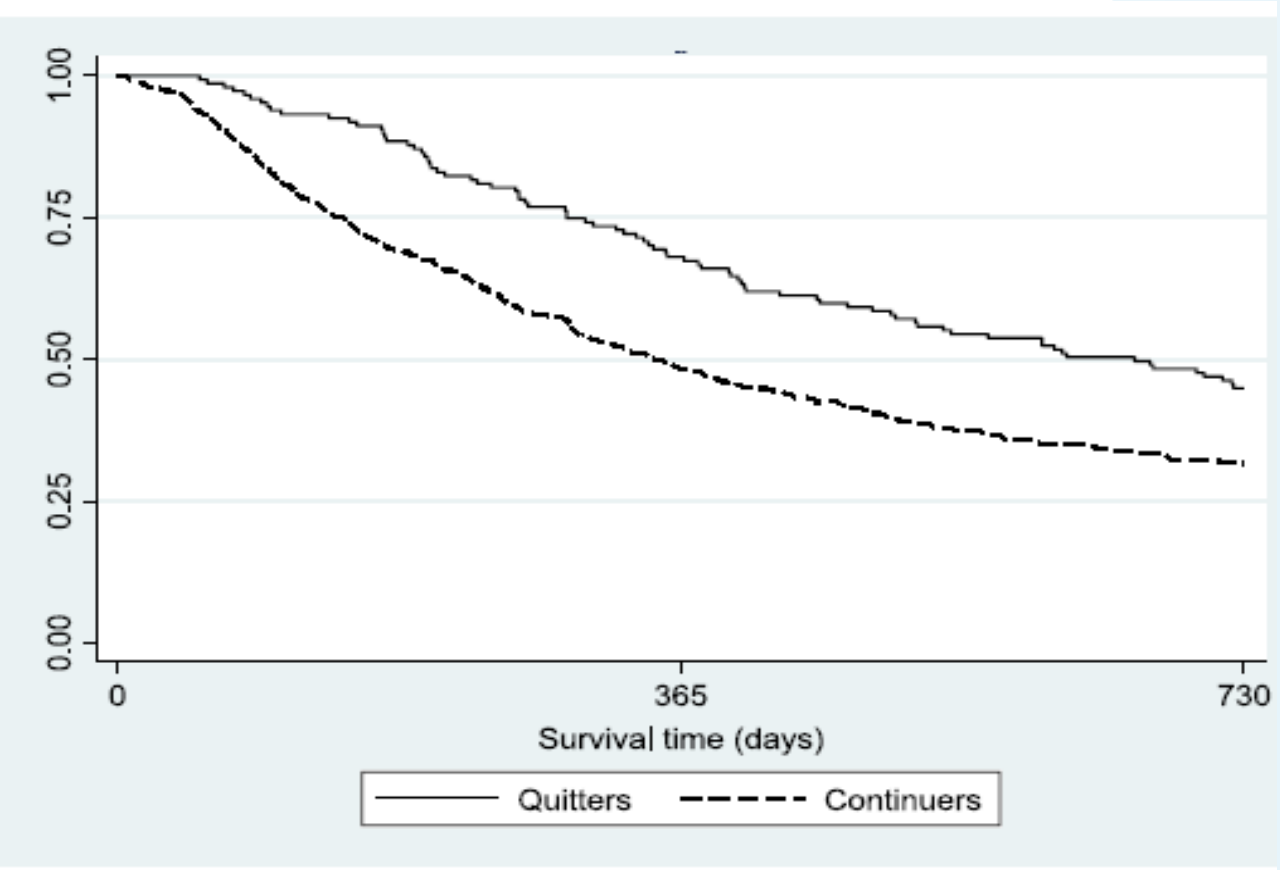
- 2751 NSCLC patients/ 646 current smokers at diagnosis; > 100 cigarettes in their lifetime, reported smoking within 30 days of diagnosis or exhaled ≥ 10 ppm carbon monoxide at any follow-up
- Current tobacco users offered smoking cessation advice and treatments according to national guidelines; Patients followed for up to two years or until death

Results:

- Median survival times quitters, 659 days; continuers 248 days
- After adjusting for age, sex, stage, performance status, intent of surgery, radical radiotherapy and comorbidity – hazard ratio for quitting at diagnosis 0.75 95% CI 0.58 - 0.98
- Unadjusted Kaplan-Meier survival analysis survivor functions for quitters **0.45,** 95% CI 0.37- 0.53; **continuers 0.32**, 0.28- 0.36 log rank test $p < 0.01$

Germine RE et al. Lung Cancer 2023; 186

Quitting smoking improves two-year survival after diagnosis of NSCLC

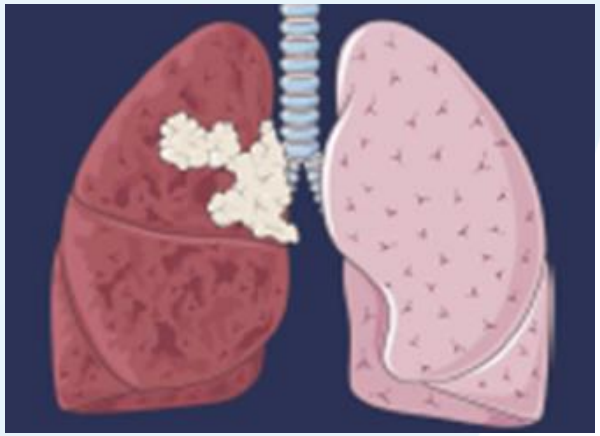


Unadjusted Kaplan-Meier survival functions

Gemine R E et al. Lung Cancer 2023; 186:1-5

Meta-analysis of smoking cessation after a lung cancer diagnosis

- 21 articles; 10, 000 lung cancer patients
- Quitting smoking at or around diagnosis: 30% lower risk of overall death (SRR: 0.71, 95% CI 0.64 – 0.80)
  - Improved overall survival (SRR 0.71, 95% CI 0.64–0.80)
  - Improved survival among patients with non-small cell LC (SRR 0.77, 95% CI 0.66–0.90)
  - Improved survival among patients with small cell LC (SRR 0.75, 95% CI 0.57–0.99)
  - Improved survival of both or unspecified histological type (SRR 0.81, 95% CI 0.68–0.96)



*SSR = Summary Relative Risk

Caini S. et al Quitting smoking at or around diagnosis improves the overall survival of lung cancer patients: A systematic review and meta-analysis J Thorac Oncol 2022 May;17 (5): 623-636

Association between quitting around diagnosis of NSCLC and survival

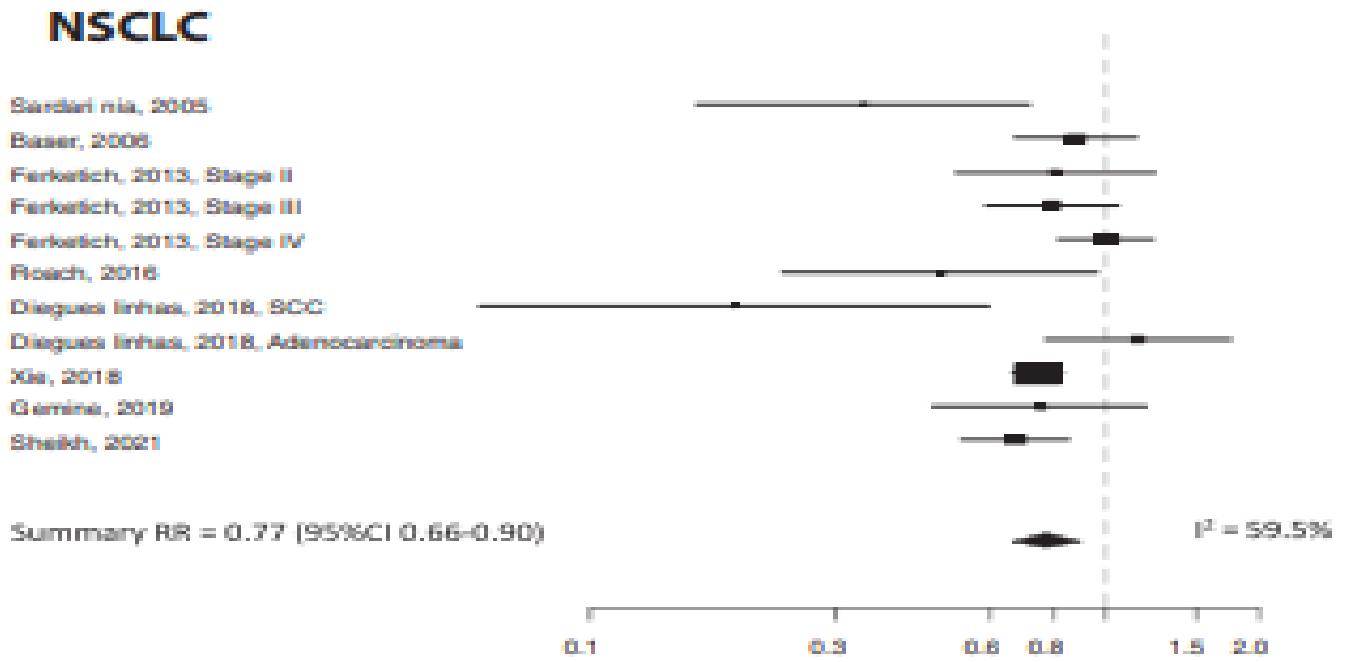


Figure 2. Forest plot for the association between quitting smoking at or around diagnosis and overall survival of patients with NSCLC. CI, confidence intervals; RR, relative risk; SCC, squamous cell carcinoma.

Caini S. et al Quitting smoking at or around diagnosis improves the overall survival of lung cancer patients: A systematic review and meta-analysis J Thorac Oncol 2022 May;17 (5): 623-636

Importance of Intensity and Timing of Smoking Cessation in Cancer Patients

Cinciripini PM, et al. Survival Outcomes of an Early Intervention Smoking Cessation Treatment After a Cancer Diagnosis. *JAMA Oncol.* Published online October 31, 2024. doi:10.1001/jamaoncol.2024.4890

MD Anderson Tobacco Treatment Program

- Prospective cohort study
- N = 4526 currently smoking cancer patients (782 lung cancer 17.3%)
- Automatic referral using electronic health records
- TTP consisted of individualized smoking cessation counselling, over-the-counter and prescription pharmacotherapy and integrated process of assessment and treatment of mental health conditions and other psychosocial concerns
- Cessation treatment between Jan 1, 2006 and March 3 2022
- Initial in-person consultation (60 – 90 minutes), plus 6 to 8 subsequent follow-up treatment sessions (60 to 45 minutes) conducted over an 8 to 12 week period
- 95% of sessions were conducted by telephone

Early intervention smoking cessation treatment

- Overall abstinence rates across the ITT sample were 42% at 3 months, 40% at 6 months and 36% at 9 months
- Abstinence from tobacco smoking at 3, 6 and 9 months after start of tobacco treatment reduced mortality across all cancer types by 26%, 22%, 16% respectively.
- Patients who received tobacco treatment within 6 months of cancer diagnosis benefited from extended survival (1.8 years) when abstinent at 3 months vs. patients who continued to smoke.

Timing and intensity of smoking cessation

Findings demonstrate the importance of receiving evidence-based tobacco treatment (tailored intervention and pharmacotherapy) as early as possible following cancer diagnosis to support quitting as soon as possible

Questions?

Thank you for listening

Any questions or comments?