Konsekvenser av røyking hos kreftpasienter

René van Helvoirt

Senter for kreftbehandling

Sørlandet sykehus

Røyking og sykdom, 1900-2000

- Dr Angel Roffo (1882-1947), Buenos Aires, var den første legen som publiserte om karsinogenitet av tobakk

- 1950: British Medical Journal publication, R. Doll og B. Hill: 'Smoking is an important cause of lung cancer'

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SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

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In England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, in the quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 9,287, or roughly fifteenfold. This remarkable increase is, of course, out of all proportion to the increase of population—both in total and, particularly, in its older age groups. Stocks (1947), using standardized death rates to allow for these population changes, shows the following trend: rate per 100,000 in 1901–20, males 1.1, females 0.7; rate per 100,000 in 1936–9, males 10.6, females 2.5. The rise seems to have been particularly rapid since the end of the first world war; between 1921–30 and 1940–4 the death rate of men at ages 45 and over increased sixfold and of women of the same ages approximately threefold. This increase is still continuing. It has occurred, too, in Switzerland, Denmark, the U.S.A., Canada, and Australia, and has been reported from Turkey and Japan.

Many writers have studied these changes, considering whether they denote a real increase in the incidence of the disease or are due merely to improved standards of diagnosis. Some believe that the latter factor can be regarded as wholly, or at least mainly, responsible—for example, Willis (1948), Clemmesen and Bonk (1947), and Steiner (1944). On the other hand, Kennaway and Kennaway (1947) and Stocks (1947) have given good reasons for believing that the rise is at least partly real. The latter, for instance, has pointed out that "the increase of certified respiratory cancer mortality during the past 20 years has been as rapid in country districts as in the cities with the best diagnostic facilities, a fact which does not support the view that such increase merely reflects improved diagnosis of cases previously certified as bronchitis or other respiratory affections." He also draws attention to differences in mortality between some of the large cities of England and Wales, differences which it is difficult to explain in terms of diagnostic standards.

The large and continued increase in the recorded deaths even within the last five years, both in the national figures and in those from teaching hospitals, also makes it hard to believe that improved diagnosis is entirely responsible. In short, there is sufficient reason to reject that factor as the whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

Possible Causes of the Increase

Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (2) the smoking of tobacco. Some characteristics of the former have certainly become more prevalent in the last 50 years, and there is also no doubt that the smoking of cigarettes has greatly increased. Such associated changes in time can, however, be no more than suggestive, and until recently there has been singularly little more direct evidence. That evidence, based upon clinical experience and records, relates mainly to the use of tobacco. For instance, in Germany, Müller (1939) found that only 3 out of 86 male patients with cancer of the lung were non-smokers, while 56 were heavy smokers, and, in contrast, among 86 "healthy men of the same age groups" there were 14 non-smokers and only 31 heavy smokers. Similarly, in America, Schrek and his co-workers (1950) reported that 14·6% of 82 male patients with cancer of the lung were non-smokers, against 23·9% of 522 male patients admitted with cancer of sites other than the upper respiratory and digestive tracts. In this country, Thelwall Jones (1949—personal communication) found 8 non-smokers in 82 patients with proved carcinoma of the lung, compared with 11 in a corresponding group of patients with diseases other than cancer; this difference is slight, but it is more striking that there were 28 heavy smokers in the cancer group, against 14 in the comparative group.

Clearly none of these small-scale inquiries can be accepted as conclusive, but they all point in the same direction. Their evidence has now been borne out by the results of a large-scale inquiry undertaken in the U.S.A. by Wynder and Graham (1950).

Wynder and Graham found that of 605 men with epidermoid, undifferentiated, or histologically unclassified types of bronchial carcinoma only 1·3% were "non-smokers"—that is, had averaged less than one cigarette a day for the last 20 years—whereas 51·2% of them had smoked more than 20 cigarettes a day over the same

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Røyking og sykdom, 1900-2000

- 1964: Surgeon General Report 'Smoking and health': *Røyking er kausal relatert til lungekreft*

- 1964: Sigarett industrien blomstrer:
  - USA: 4000 solgte sigaretter per voksen per år
  - 60 millioner dollar brukt på markedsføring

Røyking og sykdom, 1900-2000

- 1970-71: helseadvarsler på tobakk og starten av forbud mot tobakksannonser på radio og TV

- 1979: ny Surgeon General Report: *Smoking is far more dangerous than was supposed in 1964*

Røyking og sykdom, 1900-2000

- 1980: Passiv røyking er kausal relatert til lungekreft

- 1984: Nicotine tyggegummi kom på markedet

- 2000: USD 9592 millioner brukt på markedsføring

  (ca NOK 80 milliarder……)

OnkoLiS

Røyking og kreft

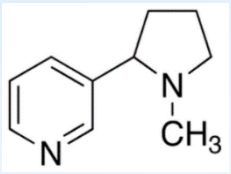
- Røyking er kausal relatert til kreft i:

Blære	Nyre
Bryst	Ovarium
Cervix uteri	Pankreas
Colon	Rectum
Lever	Ventrikkel
Leukemi	Øre, nese, hals
Lunge	Øsofagus

30% av alle kreftdødsfall er en følge av røyking!

Sammensetningen av tobakksrøyk

- Røyk inneholder ca 7000 forskjellige stoffer; nikotin er det mest avhengighetsskapende



- 60 stoffer i røyk er bekreftet karsinogen

- Filtersigaretter og light sigaretter førte til en økning i lungekrefttilfeller:

  > flere per dag og dypere inhalering

Surg. Gen. Report 2014: Kreft + røyking

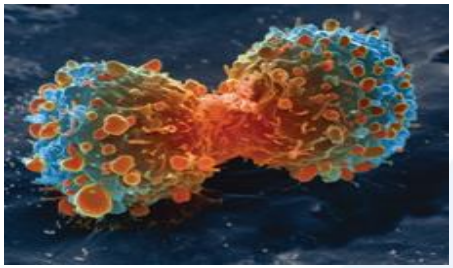
- Kreftpasienter som røyker har:
  - Større dødelighet
  - Større risiko for tilbakefall av kreften
  - Lavere effekt av medikamentell- og strålebehandling
  - Større behandlingsrelatert akutt- og sentoksisitet
  - Større risiko for en annen kreftsykdom

Kreft og røyking

Hva skjer på celle-/vevsnivå?

1. Mer aggressiv deling

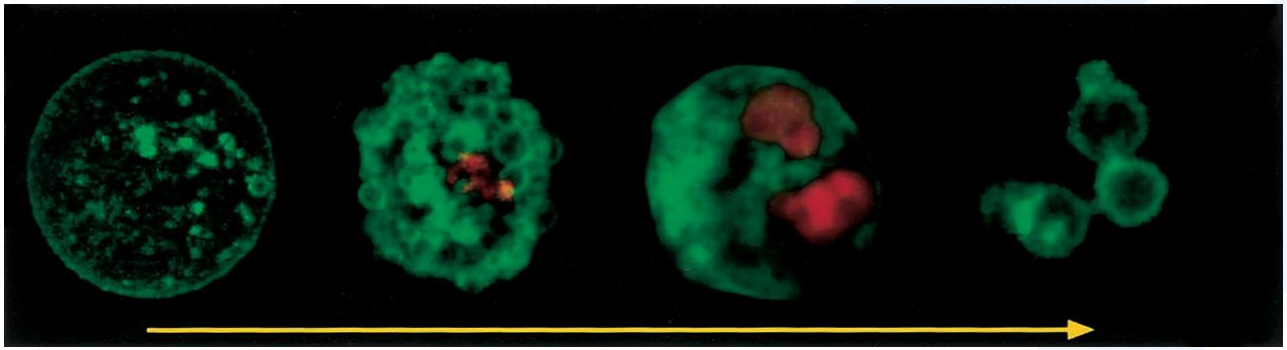
- Cellulære reseptor signalveier involvert i celledeling, blir påvirket av tobakksrøyk



- Resultatet er at cancercellene blir mer malign og deler raskere

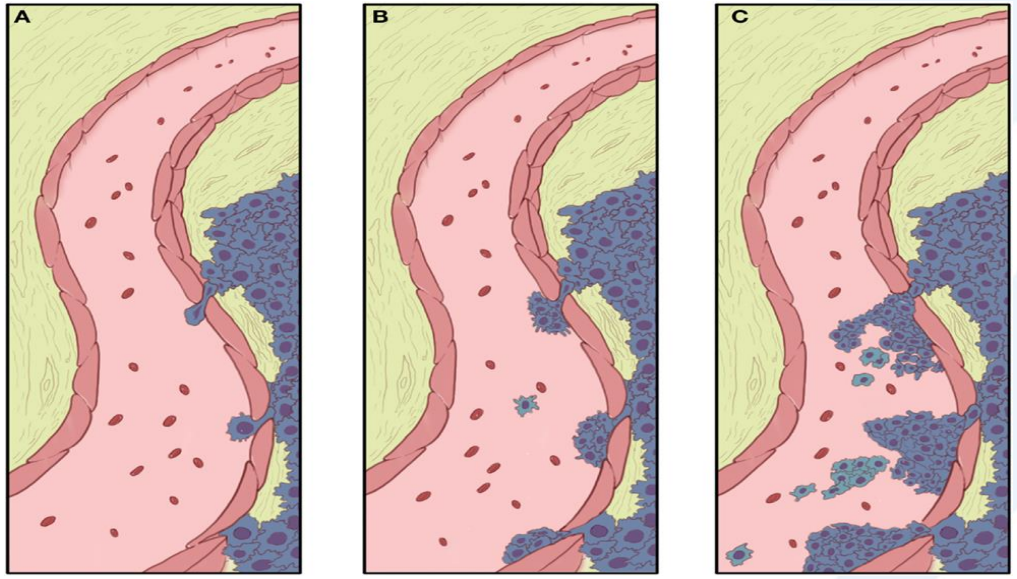
2. Mindre programmert celledød

- Eksponering til tobakksrøyk fører til mindre celledød (apoptosis) og utvikling av en pro-survival celletype



3. Mer invasjon / spredning

- Kreftceller som er utsatt for røyk endrer seg til en celletype som er mer invaderende og gir raskere spredning



4. Påvirkning av immunsystemet

- Immunsystemet blir mindre effektiv

> Gunstig klima for tumorcellene

> Ugunstig klima for friskt vev

5. Enzyminduksjon og reseptor effekter

- Tobakksrøyk induserer enzymer som er aktive med nedbryting av cellegift

↓

høyere enzymaktivitet gir lavere blodspeil

- Effekter på membrannivå gir dårligere virkning av for eksempel TKI

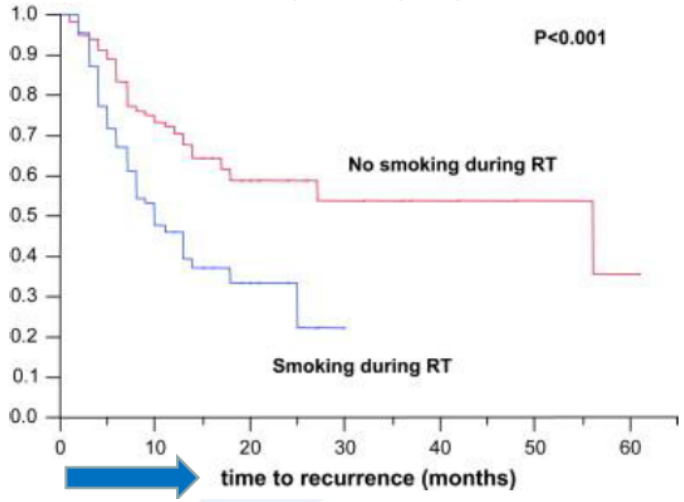
6. Dårligere effekt av strålebehandling

- In vitro cellekulturer: ved stråling under røyk dør det færre celler

- In vivo: lungecancer

Lokal kontroll, 181 pts	1 år	2 år
Røykere	46%	34%
Ikke røykere	71%	58%

Rades D, Effect of Smoking During Radiotherapy in Patients Irradiated for NSCLC
Int J Rad Onc, 2008, 71;4:1134–1142



Hva er de kliniske konsekvensene?

- Økt overall dødelighet: RR 1,5 - 5
- Økt kreftrelatert dødelighet: RR 1,5 - 3
- Økt risiko for tilbakefall: RR 1,4 - 2
- Økt risiko for en annen kreft: RR 2 – 32 (!)
  - Strålebehandling: ↑↑ stråleindusert sekundærcancer

Hva er de kliniske konsekvensene?

- Økt behandlingsrelatert toksisitet : RR 2 – 9

  Eksempel:

Prostataca strålebeh	aldri- / ex-røykere	røykere
tarmkramper	2%	18%
urge	20%	53%
diare	9%	24%
kontinensproblemer	5%	23%

- Økt operasjonsmortalitet og morbiditet

Gevinst av røykeslutt?

- Risikoen for død og komplikasjoner hos pasienter som sluttet å røyke før start av behandlingen forblir høyere enn hos aldri røykere

- Men risikoen er signifikant lavere enn hos fortsatt røykere:

  å slutte gir 30-50% risikoreduksjon

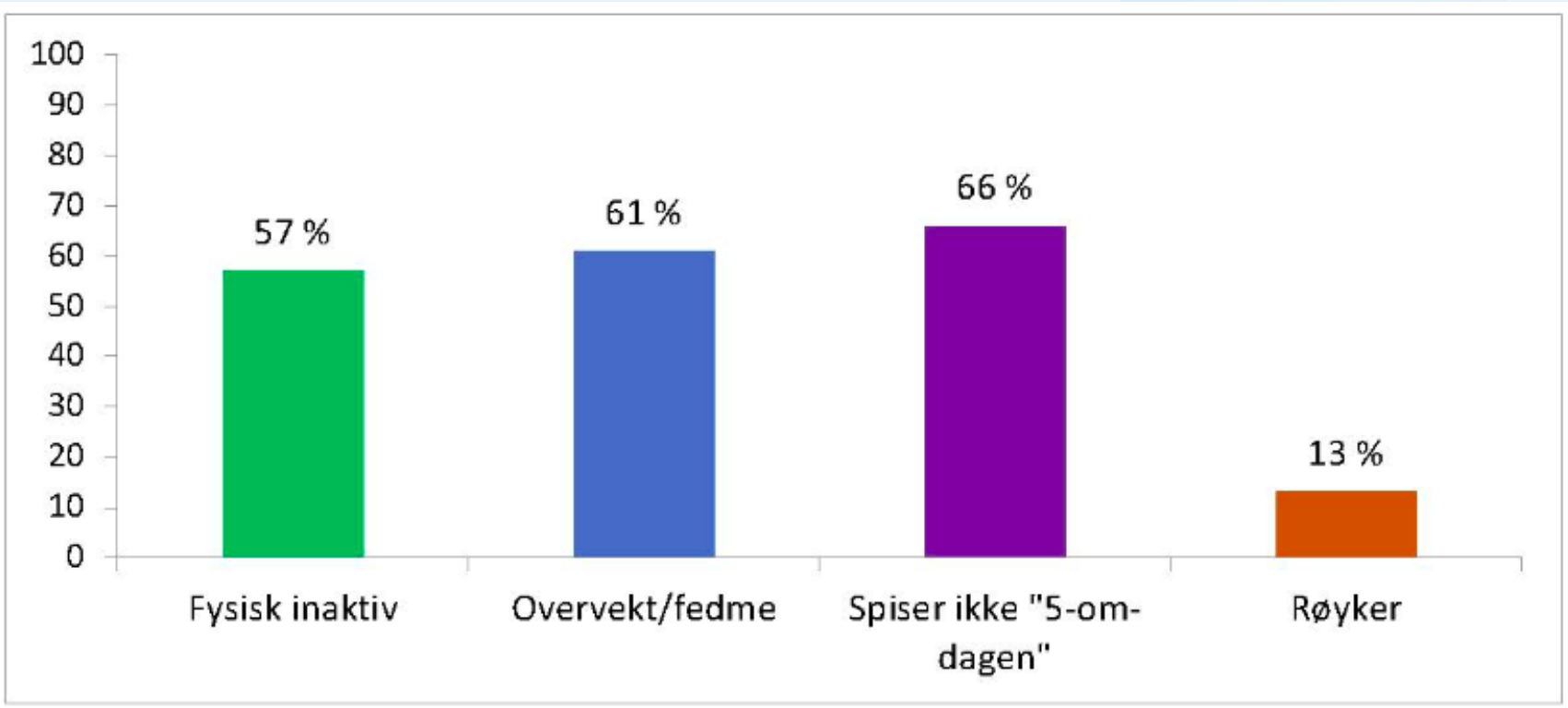
Bonus: økt QoL og PS

- Høyere overall Quality of life etter røykeslutt
- Høyere Performance status etter røykeslutt
- Dette gjelder også for palliative pasienter!

Hvor mange klarer å slutte?

- Opptil 50% av pasientene slutter når de får kreftdiagnosen, men mange dessverre bare midlertidig
- En anbefaling alene, får ikke mer enn 15-25% til å slutte varig
- Evidensbasert individuelt rettet røykeslutt veiledning kan doble dette > suksess oppnås hos 40-50%

% med livsstilsendring > 5 år etter kreftdiagnosen (NED)



Figur 1: Estimert andel kreftoverlevere som følger anbefalinger for en sunn livsstil, tall hentet fra Tollosa et al (29).

OnkoLiS

Metoder for å oppnå røykeslutt

- Kognitiv adferd intervensjon
- Nikotin erstatning (plaster, tyggegummi, spray)
- Varenicline (Champix®)
  - partiell nikotinreseptorer agonist
- (Snus eller E-sig)