CLINICAL RESEARCH STUDY

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# Smoking Status and Incidence of Cancer After Myocardial Infarction: A Follow-Up Study of over 20 Years

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## ABSTRACT

**OBJECTIVES:** We evaluated long-term incidence of cancer after myocardial infarction among current, former, and never smokers, and assessed whether reducing cigarette consumption is associated with decreased cancer risk.

**METHODS:** Consecutive patients aged ≤65 years discharged from 8 hospitals in central Israel after first myocardial infarction in 1992-1993 were followed for cancer and death. Extensive data including smoking habits were obtained at the index hospitalization and 4 time points during follow-up. Survival methods were applied to assess the hazard ratios (HRs) for cancer associated with smoking categories.

**RESULTS:** Included in the study were 1486 cancer-free participants (mean age, 54 years; 81% men), among whom 787 were current smokers at baseline (average daily cigarette consumption = 29). Smokers were younger than nonsmokers and more likely to be male and of lower socioeconomic status. Over a median follow-up of 21.4 years, 273 (18.4%) patients developed cancer. Baseline smoking was associated with a ~40% excess adjusted risk of cancer; ~25% after accounting for death as a competing event. Considering changes in smoking during follow-up, the excess risk was confined to persistent smokers (adjusted HR 1.75; 95% confidence interval [CI], 1.22-2.50), whereas post- (HR 1.14; 95% CI, 0.80-1.62) and pre-myocardial infarction quitters (HR 1.02; 95% CI, 0.71-1.47) were comparable with never smokers. Among persistent smokers, each reduction of 10 cigarettes relative to pre-myocardial infarction consumption was associated with a ~10% reduced adjusted risk.

**CONCLUSION:** Among young survivors of first myocardial infarction followed-up longitudinally, smoking cessation is associated with lower risk of cancer. Reducing consumption among smokers may also be beneficial.

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**KEYWORDS:** Cancer; Cigarette reduction; Follow-up; Longitudinal studies; Myocardial infarction; Secondary prevention; Smoking; Tobacco

Smoking is a risk factor for a multitude of ailments including multiple cancers and cardiovascular diseases,[1-4] the 2 leading causes of death in the world.[5-7] Recent evidence suggests a higher cancer incidence among patients with preexisting cardiovascular disease[8-11] including heart failure[12-14] and myocardial infarction,[9,15] as compared with the general population. Moreover, in the past decades, a shift in the cause of death after myocardial infarction from cardiovascular to noncardiovascular disease has been documented,[16-18] with cancer becoming a main cause.[16,17] In this context, a series of molecular pathways of disease development and progression common to atherosclerosis and cancer suggest that these diseases are more closely related than previously believed.[19,20] This includes a number of similar risk factors (eg, obesity, diabetes mellitus) and shared features such as chronic inflammation and oxidative stress.[20]

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Smokers are overrepresented among cardiac patients and face a worse prognosis than nonsmokers.[21-23] Yet, smoking cessation after myocardial infarction instantly improves cardiovascular disease outcomes.[21,24,25] For cancer incidence in general, the decline in risk attributable to smoking cessation may take longer, and even after decades of abstinence, the risk may not reach that of never smokers.[2,26] To this end, data on the association between smoking cessation prior to or after myocardial infarction and long-term cancer incidence are scarce.[11]

Although a dose-response relationship has been demonstrated between smoking intensity and various adverse health outcomes,[2,4,27,28] uncertainty exists as to whether cigarette reduction—cutting down the number of cigarettes smoked per day—is advantageous. Indeed, there are conflicting findings as to the effectiveness of cigarette reduction with regard to all-cause mortality and various cancer outcomes.[21,29-35]

**CLINICAL SIGNIFICANCE**

- In a longitudinal study involving 1500 young patients with first acute myocardial infarction, we compared long-term cancer incidence according to smoking status, as repeatedly assessed at 5 time points during follow-up.
- Quitting smoking after myocardial infarction, as well as quitting prior to the infarct, was associated with a significant improvement in cancer-free survival.
- Among smokers who were unable to quit, reducing intensity was associated with a modest decline in cancer risk.

Using data from a prospective, population-based cohort study of patients with incident (first-ever) myocardial infarction with repeated assessments of smoking, our goals were: 1) to evaluate long-term cancer incidence of never smokers, pre- and post-myocardial infarction quitters, and persistent smokers; and 2) to examine whether cigarette reduction among smokers is associated with lower cancer risk.

## METHODS

### Study Design and Setting

The Israel Study of First Acute Myocardial Infarction is a longitudinal prospective investigation of the role of sociodemographic, medical, and psychosocial variables measured in relatively young patients hospitalized with first myocardial infarction in long-term clinical outcomes, psychosocial adjustment, and quality of life.[21,36,37] Between February 15, 1992 and February 15, 1993, a total of 1626 consecutive patients aged 65 years or less were admitted to 8 Israeli medical centers. These hospitals provide care to the entire population of central Israel. Of these patients, 81 died during hospitalization, 24 withdrew consent, and 35 had a history of cancer prior to study entry and were therefore excluded, leaving 1486 participants in the study.

The diagnosis of myocardial infarction was established by the presence of at least 2 of the following criteria: 1) characteristic chest pain lasting at least 20 minutes; 2) creatine kinase elevation $\geq$1.5 times the upper limit of normal or creatine kinase MB fraction >5% when simultaneous reference creatine kinase levels exceeded the upper limit of normal; and 3) electrocardiographic changes compatible with Q wave or non-Q-wave myocardial infarction. Subjects with prior infarction were excluded. All diagnoses were verified by a senior cardiologist.

Data at study entry and during follow-up were obtained through structured interviews, standard questionnaires, and review of the entire medical record. Participants were interviewed 5 times: during the index hospitalization prior to discharge (T1) and after 3-6 months (T2), 1-2 years (T3), 5 years (T4), and 10-13 years (T5). All aspects of the study were approved by the appropriate institutional review boards.

### Smoking Status Assessment

Data on smoking were obtained using structured interviews. Smoking habits, including intensity (number of cigarettes smoked per day) and duration (years of smoking), were reported at T1, with the former reassessed at all follow-up interviews (T2-T5). In T1, patients were asked about their smoking habits prior to the myocardial infarction. In the following interviews, the questions referred to both present smoking behavior and smoking habits since last interview. Pre-myocardial infarction quitting was defined as abstinence for more than 6 months prior to the event in previous smokers.[38] Intermittent smoking between interviews was classified as smoking.[39] Cigar and pipe smoking was infrequent (eg, only 7 participants [0.6%] at T5) in this cohort.

### Sociodemographic Variables

Demographic and socioeconomic measures, considered as potential confounding factors for the current analysis, were self-reported and included ethnicity (categorized as Israeli born [Jews], Mizrachi, Ashkenazi, and other/unknown[40]), education (years of schooling completed), and family income relative to the national average (categorized as below average, average, and above average). Neighborhood socioeconomic status, recently reported to be associated with cancer incidence,[41] was also considered. Neighborhood socioeconomic status was estimated through a composite census-derived index developed by the Israel Central Bureau of Statistics.[37]

### Clinical Variables

Body mass index was categorized as <25, 25-30, and >30 kg/m$^2$. Diabetes mellitus, hypertension, and