Smoking and Mortality — Beyond Established Causes


Background. Mortality among current smokers is 2 to 3 times as high as that among persons who never smoked. Most of this excess mortality is believed to be explained by 21 common diseases that have been formally established as caused by cigarette smoking and are included in official estimates of smoking-attributable mortality in the United States. However, if smoking causes additional diseases, these official estimates may significantly underestimate the number of deaths attributable to smoking.

Methods. We pooled data from five contemporary U.S. cohort studies including 421,378 men and 532,651 women 55 years of age or older. Participants were followed from 2000 through 2011, and relative risks and 95% confidence intervals were estimated with the use of Cox proportional-hazards models adjusted for age, race, educational level, daily alcohol consumption, and cohort.

Results. During the follow-up period, there were 181,377 deaths, including 16,475 among current smokers. Overall, approximately 17% of the excess mortality among current smokers was due to associations with causes that are not currently established as attributable to smoking. These included associations between current smoking and deaths from renal failure (relative risk, 2.0; 95% confidence interval [CI], 1.7 to 2.3), intestinal ischemia (relative risk, 6.0; 95% CI, 4.5 to 8.1), hypertensive heart disease (relative risk, 2.4; 95% CI, 1.9 to 3.0), infections (relative risk, 2.3; 95% CI, 2.0 to 2.7), various respiratory diseases (relative risk, 2.0; 95% CI, 1.6 to 2.4), breast cancer (relative risk, 1.3; 95% CI, 1.2 to 1.5), and prostate cancer (relative risk, 1.4; 95% CI, 1.2 to 1.7). Among former smokers, the relative risk for each of these outcomes declined as the number of years since quitting increased.

Conclusions. A substantial portion of the excess mortality among current smokers between 2000 and 2011 was due to associations with diseases that have not been formally established as caused by smoking. These associations should be investigated further and, when appropriate, taken into account when the mortality burden of smoking is investigated. (Funded by the American Cancer Society.)

Cytisine versus Nicotine for Smoking Cessation

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Background. Placebo-controlled trials indicate that cytisine, a partial agonist that binds the nicotinic acetylcholine receptor and is used for smoking cessation, almost doubles the chances of quitting at 6 months. We investigated whether cytisine was at least as effective as nicotine-replacement therapy in helping smokers to quit.

Methods. We conducted a pragmatic, open-label, noninferiority trial in New Zealand in which 1310 adult daily smokers who were motivated to quit and called the national quitline were randomly assigned in a 1:1 ratio to receive cytisine for 25 days or nicotine-replacement therapy for 8 weeks. Cytisine was provided by mail, free of charge, and nicotine-replacement therapy was provided through vouchers for low-cost patches along with gum or lozenges. Low-intensity, telephone-delivered behavioral support was provided to both groups through the quitline. The primary outcome was self-reported continuous abstinence at 1 month.

Results. At 1 month, continuous abstinence from smoking was reported for 40% of participants receiving cytisine (264 of 655) and 31% of participants receiving nicotine-replacement therapy (203 of 655), for a difference of 9.3 percentage points (95% confidence interval, 4.2 to 14.5). The effectiveness of cytisine for continuous abstinence was superior to that of nicotine-replacement therapy at 1 week, 2 months, and 6 months. In a prespecified subgroup analysis of the primary outcome, cytisine was superior to nicotine-replacement therapy among women and noninferior among men. Self-reported adverse events over 6 months occurred more frequently in the cytisine group (288 events among 204 participants) than in the group receiving nicotine-replacement therapy (174 events among 134 participants); adverse events were primarily nausea and vomiting and sleep disorders.
Conclusions. When combined with brief behavioral support, cytisine was found to be superior to nicotine-replacement therapy in helping smokers quit smoking, but it was associated with a higher frequency of self-reported adverse events. (Funded by the Health Research Council of New Zealand; Australian New Zealand Clinical Trials Registry number, ACTRN12610000590066.)

First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer

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Background. The efficacy of the ALK inhibitor crizotinib as compared with standard chemotherapy as first-line treatment for advanced ALK-positive non–small-cell lung cancer (NSCLC) is unknown.

Methods. We conducted an open-label, phase 3 trial comparing crizotinib with chemotherapy in 343 patients with advanced ALK-positive nonsquamous NSCLC who had received no previous systemic treatment for advanced disease. Patients were randomly assigned to receive oral crizotinib at a dose of 250 mg twice daily or to receive intravenous chemotherapy (pemetrexed, 500 mg per square meter of body-surface area, plus either cisplatin, 75 mg per square meter, or carboplatin, target area under the curve of 5 to 6 mg per milliliter per minute) every 3 weeks for up to six cycles. Crossover to crizotinib treatment after disease progression was permitted for patients receiving chemotherapy. The primary end point was progression-free survival as assessed by independent radiologic review.

Results. Progression-free survival was significantly longer with crizotinib than with chemotherapy (median, 10.9 months vs. 7.0 months; hazard ratio for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001). Objective response rates were 74% and 45%, respectively (P<0.001). Median overall survival was not reached in either group (hazard ratio for death with crizotinib, 0.82; 95% CI, 0.54 to 1.26; P=0.36); the probability of 1-year survival was 84% with crizotinib and 79% with chemotherapy. The most common adverse events with crizotinib were vision disorders, diarrhea, nausea, and edema, and the most common events with chemotherapy were nausea, fatigue, vomiting, and decreased appetite. As compared with chemotherapy, crizotinib was associated with greater reduction in lung cancer symptoms and greater improvement in quality of life.

Conclusions. Crizotinib was superior to standard first-line pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced ALK-positive NSCLC. (Funded by Pfizer; PROFILE 1014 ClinicalTrials.gov number, NCT01154140.)

Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline and Expert Panel Report


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Objective. Choices of pharmacologic therapies for pulmonary arterial hypertension (PAH) are ideally guided by high-level evidence. The objective of this guideline is to provide clinicians advice regarding pharmacologic therapy for adult patients with PAH as informed by available evidence.

Methods. This guideline was based on systematic reviews of English language evidence published between 1990 and November 2013, identified using the MEDLINE and Cochrane Library databases. The strength of available evidence was graded using the Grades of Recommendations, Assessment, Development, and Evaluation methodology. Guideline recommendations, or consensus statements when available evidence was insufficient to support recommendations, were developed using a modified Delphi technique to achieve consensus.

Results. Available evidence is limited in its ability to support high-level recommendations. Therefore, we drafted consensus statements to address many clinical questions regarding pharmacotherapy for patients with PAH. A total of 79 recommendations or consensus statements were adopted and graded.

Conclusions. Clinical decisions regarding pharmacotherapy for PAH should be guided by high-
A Preliminary Quality of Life Questionnaire-Bronchiectasis: A Patient-Reported Outcome Measure for Bronchiectasis

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Background. The Quality of Life Questionnaire-Bronchiectasis (QOL-B) is the first disease-specific, patient-reported outcome measure for patients with bronchiectasis. Content validity, cognitive testing, responsivity to open-label treatment, and psychometric analyses are presented.

Methods. Reviews of literature, existing measures, and physician input were used to generate the initial QOL-B. Modifications following preliminary cognitive testing (N = 35 patients with bronchiectasis) generated version (V) 1.0. An open-ended patient interview study (N = 28) provided additional information and was content analyzed to derive saturation matrices, which summarized all disease-related topics mentioned by each participant. This resulted in QOL-B V2.0. Psychometric analyses were carried out using results from an open-label phase 2 trial, in which 89 patients were enrolled and treated with aztreonam for inhalation solution. Responsivity to open-label treatment was observed. Additional analyses generated QOL-B V3.0, with 37 items on eight scales: respiratory symptoms; physical, role, emotional, and social functioning; vitality; health perceptions; and treatment burden. For each scale, scores are standardized on a 0-to-100-point scale; higher scores indicate better health-related quality of life. No total score is calculated. A final cognitive testing study (N = 40) resulted in a minor change to one social functioning scale item (QOL-B V3.1).

Results. Content validity, cognitive testing, responsivity to open-label treatment, and initial psychometric analyses supported QOL-B items and structure.

Conclusions. This interim QOL-B is a promising tool for evaluating the efficacy of new therapies for patients with bronchiectasis and for measuring symptoms, functioning, and quality of life in these patients on a routine basis. A final psychometric validation study is needed and is forthcoming.

Trial Registry. ClinicalTrials.gov; No.: NCT00805025; URL: www.clinicaltrials.gov

Standardizing the Analysis of Physical Activity in Patients With COPD Following a Pulmonary Rehabilitation Program

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Background. There is a wide variability in measurement methodology of physical activity. This study investigated the effect of different analysis techniques on the statistical power of physical activity outcomes after pulmonary rehabilitation.

Methods. Physical activity was measured with an activity monitor armband in 57 patients with COPD (mean ± SD age, 66 ± 7 years; FEV1, 46 ± 17% predicted) before and after 3 months of pulmonary rehabilitation. The choice of the outcome (daily number of steps [STEPS], time spent in at least moderate physical activity [TMA], mean metabolic equivalents of task level [METS], and activity time [ACT]), impact of weekends, number of days of assessment, postprocessing techniques, and influence of duration of daylight time (DT) on the sample size to achieve a power of 0.8 were investigated.

Results. The STEPS and ACT (1.6-2.3 metabolic equivalents of task) were the most sensitive outcomes. Excluding weekends decreased the sample size for STEPS (83 vs 56), TMA (160 vs 148), and METS (251 vs 207). Using 4 weekdays (STEPS and TMA) or 5 weekdays (METS) rendered the lowest sample size. Excluding days with < 8 h wearing time reduced the sample size for STEPS (56 vs 51). Differences in DT were an important confounder.

Conclusions. Changes in physical activity following pulmonary rehabilitation are best measured for 4 weekdays, including only days with at least 8 h of
Background. Obesity has been associated with worse asthma control. Depression has also been shown to be disproportionately prevalent among patients with asthma and among patients with obesity. However, no studies have examined the mediating effect of depression on the obesity-asthma relationship. This study examined the extent to which depressive symptoms may mediate the obesity-asthma relationship in an adult sample.

Methods. A total of 798 patients with physician-diagnosed asthma were recruited from the outpatient asthma clinic at Hôpital du Sacré-Cœur de Montréal. Patients provided demographic and medical history information and completed a battery of questionnaires, including the Beck Depression Inventory (BDI)-II and the Asthma Control Questionnaire (ACQ). BMI was calculated from self-reported height and weight.

Results. Analyses adjusted for age, sex, years of education, cohabitation, and inhaled corticosteroid dose revealed an association between BMI and ACQ ($\beta = 0.017$, $P = .026$), between BMI and BDI-II ($\beta = 0.189$, $P = .002$), and between BDI-II and ACQ ($\beta = 0.044$, $P < .001$). However, when both BDI-II and BMI were entered into the same model, BDI-II ($\beta = 0.044$, $P < .001$) but not BMI ($\beta = 0.009$, $P = .226$) remained significantly associated with ACQ.

Conclusions. The results indicate that depression and a high BMI are both associated with worse asthma control. However, consistent with our hypotheses, the relationship between BMI and worse asthma control was mediated by depressive symptoms. Future studies should examine the precise role of depressive symptoms in both weight and asthma control.

Lung Ultrasonography for the Diagnosis of Severe Neonatal Pneumonia

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Background. Lung ultrasonography is useful for the diagnosis of pneumonia in children and adults. This study investigated the lung ultrasound findings in severe neonatal pneumonia.

Methods. From September 2012 to October 2013, 80 neonates admitted to Bayi Children’s Hospital, affiliated with the Beijing Military General Hospital, were divided into two groups: 40 neonates with severe pneumonia according to their medical history, clinical manifestations, and chest radiograph findings and 40 neonates with no lung disease (control group). All subjects underwent bedside lung ultrasound examination in a quiet state. A single expert physician performed all ultrasound examinations. Findings of pleural line abnormalities, B lines, lung consolidation, air bronchograms, bilateral white lung, interstitial syndrome, lung sliding, and lung pulse were compared between the groups.

Results. The lung ultrasound findings associated with infectious pneumonia included large areas of lung consolidation with irregular margins and air bronchograms, pleural line abnormalities, and interstitial syndrome. A large area of lung consolidation with irregular margins had 100% sensitivity and 100% specificity for the diagnosis of neonatal pneumonia.

Conclusions. Lung ultrasonography is a reliable tool for diagnosing neonatal pneumonia. It is suitable for routine use in the neonatal ICU and may eventually replace chest radiography and CT scanning.