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LETTER TO THE EDITOR

Volunteer effect and compromised randomization in the Mayo Project of screening for lung cancer

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Abstract It has been confirmed recently that the volunteer effect in lung cancer screening is characterized by higher lung cancer mortality risk in self-selected screening participants. The Mayo Lung Project, the most influential trial of screening for lung cancer ever completed, was conducted in *nonvolunteer* Mayo Clinic outpatients, with a peculiar study design that rendered the randomization vulnerable to the volunteer effect. Of all nonvolunteers randomized in the Mayo Lung Project, only those allocated in the screened group were asked consent to participate in the trial. The final Mayo Lung Project report stated that 655 randomized nonvolunteers refused screening and were excluded from the study, thus documenting violation of the rule that no selection should occur after randomization. The long-term follow-up of the Mayo Lung Project showed an enigmatic result which has never been explained: the lung cancer mortality was 13% higher in the screening intervention group than in the control group [4.4 (95% CI 3.9–4.9) vs. 3.9 (95% CI 3.5–4.4) per 1,000 person-years; $P = 0.09$]. Such overrepresented mortality is consistent with the volunteer effect and supports the concept that the Mayo Lung Project randomization was compromised by the post-randomization self-selection of participant nonvolunteers.

Keywords Compromised randomization · Lung cancer screening · Mayo lung project · Volunteer effect

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Abbreviations

CXR	Chest X-rays
CI	Confidence interval
LC	Lung cancer
MLP	Mayo lung project

Dear Editor,

The volunteer effect has been studied extensively in screening trials for cancer of the breast, colon-rectum and prostate [1–3], but it has been scarcely investigated in the context of screening for lung cancer (LC). The Johns Hopkins Lung Project first documented that the LC mortality of volunteers screened by chest X-rays (CXR) was significantly higher than expected on the basis of two large population studies, namely the Veterans Study [observed/expected LC mortality ratio 1.72; 95% confidence interval (CI) 1.28–2.18] and the American Cancer Society Study (observed/expected LC mortality ratio 1.46; 95% CI 1.09–1.83) [4]. Recently, in a population-based study of smokers offered CXR screening we confirmed that the volunteer effect is characterized by significantly higher LC mortality risk in self-selected participants compared to nonparticipants (risk ratio 1.40; 95% CI, 1.03–1.91) [5]. The volunteer effect may bias the results of comparative LC screening studies of *nonvolunteers*, if the latter are not randomized adequately. The Mayo Lung Project (MLP), the most influential trial of CXR screening for LC [6, 7], was conducted in *nonvolunteer* Mayo Clinic outpatients with a peculiar design that rendered the randomization vulnerable.

Indeed the details of the MLP randomization, described on page 1375 in the preliminary report [8], specify that: "*the random assignment to the close-surveillance or the control group is made at the interview. Up to this point,*

the Mayo Lung Project has not been mentioned, and, if the assignment is to the control group, nothing is said of it and the interview ends. If the assignment is to the close-surveillance group, however, the interviewer explains that program to the candidate and obtains his informed consent and agreement to take part in it".

Accordingly, the MLP candidates were first randomized and subsequently only the nonvolunteers allocated in the screened group were asked consent to participate in the trial; because of that study design we hypothesize that the MLP randomization was likely compromised by the volunteer bias.

The final MLP report stated that 655 randomized nonvolunteers refused screening and were excluded from the study [9], thus documenting violation of the rule that no selection should occur after randomization. After such selection and exclusion of candidates, an important methodological weakness, there is no guarantee that the screening and control groups at baseline were well matched for all known and unknown LC risks [10]. Notably, the extended follow-up of the MLP showed two puzzling results: (1) in 16 years after the end of screening (1983–1999) the total number of newly diagnosed LCs was 11% greater in the screened group than in controls (379 vs. 340) [11], an excess certainly not attributable to screening overdiagnosis; (2) the LC mortality was 13% higher in the screening intervention group than in the control group [4.4 (95% CI 3.9–4.9) vs. 3.9 (95% CI 3.5–4.4) per 1,000 person-years; $P = 0.09$] [12]. These enigmatic results are consistent with the volunteer effect in the LC screening group; moreover, they support the concept that the documented post-randomization selection of nonvolunteers compromised the MLP randomization.

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