Effectiveness of Screening for Colorectal Cancer with FOBT in Finland

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Supplementary Appendix

In the estimation of the excess mortality rate ratio and its confidence interval, we followed van Leeuwen et al. (1 and 2). The two excess mortality rates are presented as $m_i = e_i/n_i$, where i is the study arm ($i = 1$: screening arm and $i = 2$: control arm), e_i is arm-specific excess number of deaths and n_i is arm-specific number of observed person-years.

The excess number of deaths is the difference between the observed number d_i and the expected number d_i^* of deaths from any cause among the N_i CRC patients:

$$e_i = d_i - d_i^*.$$

Differences in the background mortality rates among attendees and non-attendees were taken into account by stratifying the patients in the screening arm according to their attendance status at diagnosis (N_{ip} patients had participated at least once before the diagnosis, and N_{in} patients had not participated). In the following formulae, subscript $1p$ denotes attendees and $1n$ denotes non-attendees. In the screening arm, the excess number e_1 of deaths is the sum of the excess number e_{1p} in attendees and the excess number e_{1n} in non-attendees, i.e.,

$$e_1 = e_{1p} + e_{1n} = d_{1p} - d_{1p}^* + d_{1n} - d_{1n}^*.$$

The expected numbers of deaths d_{1p}^*, d_{1n}^* and d_2^* are calculated based on the assumption that the patients would have the same mortality rates (stratified by sex, age, calendar year and study arm and, in the screening arm, also by attendance status) as persons who were not diagnosed with CRC in the randomized population.

The numbers of deaths d_i and d_i^* are mathematically related to the number N_i of CRC patients as

$$d_i = N_i q_i \text{ and } d_i^* = N_i q_i^*$$

where q_i and q_i^* are the observed and the expected death proportions, respectively. In the estimation of the variance, neither d_i nor d_i^* can be regarded to be constant as they depend on N_i, a Poisson-distributed random variable. The death proportion q_i is assumed to be a parameter of a binomial distribution with radix N_i, and the expected death proportion q_i^* is regarded to be fixed as it is based on the large total number of deaths among persons who were not diagnosed with CRC in the randomized population.

Accounting for participation the excess mortality rate ratio can be written as

$$\frac{m_1}{m_2} = \frac{d_{1p} - d_{1p}^* + d_{1n} - d_{1n}^*}{d_2 - d_2^*}\frac{n_2}{n_1} = \frac{N_{1p}(q_{1p} - q_{1p}^*) + N_{1n}(q_{1n} - q_{1n}^*)}{N_2(q_2 - q_2^*)}\frac{n_2}{n_1} = \frac{\text{num}}{\text{den}}\frac{n_2}{n_1}.$$

The 95% confidence interval for the excess mortality rate ratio was constructed on a logarithmic scale. The variance of the logarithm of the excess mortality rate ratio can be estimated by the delta method as

$$\mathrm{Var}\left(\log\left(\frac{m_1}{m_2}\right)\right) = \frac{\mathrm{Var(num)}}{(\mathrm{num})^2} + \frac{\mathrm{Var(den)}}{(\mathrm{den})^2}.$$

The $\mathrm{Var(num)}$ and $\mathrm{Var(den)}$ can be estimated as

$\mathrm{Var(num)} = N_{1p}\left[\left(q_{1p} - q_{1p}^{*}\right)^2 + q_{1p}\left(1 - q_{1p}\right)\right] + N_{1n}[(q_{1n} - q_{1n}^{*})^2 + q_{1n}(1 - q_{1n})]$ and

$\mathrm{Var(den)} = N_2[(q_2 - q_2^{*})^2 + q_2(1 - q_2)]$

Here, the Poisson assumption of N_i, constancy assumption of q_i^{*}, binomial assumption for q_i , and the delta method for the variance of a product have been made use of.

References

1. Van Leeuwen PJ, Kranse R, Hakulinen T, et al. Disease-specific mortality may underestimate the total effect of prostate cancer screening. J Med Screen 2010;17:204–10.

2. Van Leeuwen PJ, Kranse R, Hakulinen T, et al. Impacts of a population-based prostate cancer screening programme on excess total mortality rates in men with prostate cancer: a randomized controlled trial. J Med Screen 2013;20:33–8.