

Randomized Trial of Questionnaire Length

To the Editor:

We conducted a pilot study to assess the feasibility of recruiting, enrolling, and following cohort study participants through the internet. The study population comprised Danish women planning to become pregnant. One objective was to determine how length of the baseline questionnaire affected enrollment and completeness of data.

Eligible women were asked to complete a baseline enrollment questionnaire and provide their e-mail address and Central Population Registry number, a unique 10-digit number assigned to each resident of Denmark. They were then randomized to receive either a short (up to 233 questions [74%]) or long (up to 317 questions [100%]) version of the baseline questionnaire. Some questions were contingent on responses to others. Women could log out of the questionnaire and return at a later time.

Both questionnaires included demographics; menstruation and contraceptive history; height and weight; and lifestyle exposures (eg, tobacco use, alcohol and caffeine intake, and medication use). The short version included an abbreviated reproductive and medical history, including questions about sexually transmitted diseases. The long version asked for additional details about prior pregnancies, including pregnancy outcome, gestational age, and weight gain, other diseases that could affect fertility, and any prior diagnosis of infertility. Other questions included only in the long form were measurement of waist and hip circumference, menstrual cycle characteristics, infertility history of mother, night shift work, and partner and parents' education.

After 6 months, 4807 women completed the screener, of whom 3070 (64%) met the eligibility criteria. Among these, 702 (23%) did not provide their Registry number, leaving

2368 women randomly assigned to the short or long baseline questionnaire. The median times to complete the long and short questionnaires were 23 and 18 minutes, respectively. Characteristics of the 2 randomly assigned groups were similar (eTable 1).

Enrollment proportions were virtually identical for the 2 randomized groups, with 1129 of 1167 (97%) of those given the short form completing enrollment versus 1159 of 1201 (97%) of those given the long form. Few data items were missing, allowing for only small differences between the groups. For example, little information on smoking history was missing for both groups (0.3% missing in the short version vs. 0.4% in the long version), and coffee consumption was missing for 1.4% of women who received the short version and 1.2% who received the long version.

Our results indicate no important differences in enrollment or extent of missing data between those assigned a short or long version of a web-based questionnaire. Studies of the length of paper-based questionnaires have mostly indicated a modest effect of questionnaire length on response.¹⁻⁴ Other factors, including monetary incentives, recorded delivery, order of questions, or a teaser on the envelope had stronger effects on response than questionnaire length.^{1,5}

Our study participants may have been more highly motivated than other study populations, possibly obscuring effects of questionnaire length that might be more apparent in less highly motivated populations. Our short questionnaire contained 26% fewer questions than the long version, which translated into only about a 5-minute difference in the median time to complete. Thus, our findings may not apply to questionnaires that are considerably longer. Nevertheless, these results indicate that using the internet for recruitment into a prospective cohort study seems to be an attractive strategy, and that in a motivated study

population a questionnaire that takes longer than 20 minutes to complete is not necessarily a deterrent for participation.

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Breast Cancer Risk and History of Being Breast-Fed

To the Editor:

The article by Nichols et al¹ has addressed an important and complex issue. Because increasing birth order and younger maternal age are likely to be associated with lower levels of exposure to potentially carcinogenic environmental pollutants in breastmilk, the authors postulated that adult breast cancer risk would be lower in breastfed women with higher birth order, and in those breastfed by younger mothers. Their results showed that higher birth order is associated with reduced risk of breast cancer among those who were breastfed in infancy, but younger maternal age was not. Overall, breast cancer risk was substantially lower in breastfed women than formula-fed women, although the reduced risk was not apparent in the first-born women.

The authors cite breastmilk contaminated with persistent organic pollutants (POPs) as a plausible mechanism to explain their findings. However, an equally plausible and not mutually exclusive hypothesis is that exposure to infant formula (or lack of human milk) is associated with increased risk of breast cancer.

Toxic effects of POPs are orchestrated by arylhydrocarbon receptor (AhR) in the cell. AhR activation is the initial event of biologically significant exposures to POPs, which causes, among other things, cytochrome P4501A (CYP1A) induction, a biomarker of AhR activation. Therefore, we were surprised when we unexpectedly discovered that AhR is strongly activated, and CYP1A induced, in vitro by infant formula, but not by human milk.² A recent study by Blake et al³ showed that CYP1A activity is significantly higher in formula-fed infants, consistent with our data.² POPs are surely present in human milk, but the amount found in

women may not be biologically meaningful. Breastmilk is still far better than infant formula under most circumstances for many other reasons.

Because the findings by Nichols et al¹ are important, it is even more important to be interpreted in a fair and balanced manner. Many studies including ours and Nichols' have delved into the big black box. At least for now, the answers remain unclear.

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Residential Radon and Lung Cancer

To the Editor:

Residential radon exposure causes lung cancer. The International Agency for Research on Cancer declared radon as a human carcinogen in 1988.¹ Evidence for this statement is based mainly on studies in miners² and residential case-control studies.^{3,4} There are no published cohort studies assessing the relationship between residential radon exposure and the development of lung cancer.

Between 1992 and 1994, we enrolled 241 randomly selected controls in a population-based case-control

study on residential radon and lung cancer by using 1991 census data for the Santiago de Compostela Health District.⁵ Initially, 500 persons from the general population were selected through sex-stratified random sampling. Of these, 391 met the eligibility criteria and 241 were finally included (32% refused and 5% were not located after 3 attempts).

Participants younger than 35 years of age, those with previous cancers, and those who had lived fewer than 5 years in the same dwelling were excluded. All participants were personally interviewed on lung cancer risk factors, and radon concentration was measured in the main bedroom under standard conditions.

Cohort follow-up ended on 31 May 2007. For each cohort member, the vital status was assessed through 2 databases: hospital records at the Clinic University Hospital of Santiago de Compostela and the Galician Mortality Registry, which covers the whole Galician population. The survival outcomes were (a) alive, (b) death from a cause other than cancer, (c) incidence or death from cancer other than lung cancer, and (d) incidence or death from lung cancer. Radon exposure at baseline was compared among persons without cancer, those with cancer other than lung cancer, and those with lung cancer at the end of the follow-up.

We could find determine outcome status of 211 persons (88%); median follow-up was 12 years. During the follow-up, 11% (25 subjects) had developed some type of cancer, 5 additional patients had lung cancer. Tobacco consumption was similar among groups at the baseline (Table 1). The median radon concentration was 226 Bq/m³ among future lung cancer cases and 52 Bq/m³ among all others. All lung cancer cases lived in the same dwelling until the end of the follow-up. The crude relative risk for lung cancer among those exposed to radon concentrations higher than 148 Bq/m³ compared with nonexposed

TABLE 1. Baseline Cohort Characteristics and Radon Relative Risks (1992–1994)

Variable	Initial Cohort (Baseline Characteristics) n = 211	Cancer Other Than Lung Cancer n = 25	Lung Cancer n = 5
Age (%) ^a			
35–50	71 (34)	7 (28)	0 (0)
51–70	106 (50)	12 (48)	3 (60)
>70	34 (16)	6 (24)	2 (40)
Men (%)	187 (89)	19 (76)	5 (100)
Current smoking ^a (%)	77 (36)	9 (36)	2 (40)
Quartiles of lifetime smoking in thousands of packets (only for ever smokers) ^a			
25	5	2	12
50	11	11	21
75	18	17	32
Have lived >20 yr in the same residence (%)	127 (60)	52 (52)	4 (80)
Quartiles of radon concentration (Bq/m ³)			
25	30	35	85
50	52	52	226
75	117	96	729
Subjects above the EPA level (148 Bq/m ³) (%)	41 (20)	3 (12)	3 (60)
RR (CI 95%)	1.00	0.68 (0.2–2.2)	6.6 (1.2–38)

^aBaseline characteristics of those subjects who developed lung or other cancer type on the follow-up.

was 6.6 (95% confidence interval = 1.2–38), whereas the relative risk for any cancer type was 0.68 (0.2–2.2).

To our knowledge these are the first cohort data on residential radon exposure and lung cancer, and the results confirm an association. Residential radon concentration in those who developed lung cancer was 4.5-fold higher than the radon concentration in the other groups, the median concentration being far above the action level considered by EPA or European Union (148 and 200 Bq/m³, respectively).

This study has a small sample size, which does not allow a detailed analysis. Nevertheless, these are the first data of their kind and add evidence that radon concentration predicts the risk of lung cancer years before its onset. An advantage in this investigation is that the proportion of smokers was similar among the study groups, and therefore, we believe that the higher lung cancer incidence in those exposed to higher radon concentrations is not due to higher tobacco consumption.

Other researchers who have conducted residential case-control studies may be able to add to these results using larger samples.

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High Sensitivity of Children to Swimming-Associated Gastrointestinal Illness

To the Editor:

The results presented by Wade et al¹ are an important contribution to Environmental Protection Agency's (EPA) planned research to revise recreational water quality criteria.² EPA's research will provide a basis for decisions regarding public beach use and pollution control requirements nationwide.

A key issue is whether the criteria protect potentially sensitive subgroups of the beach-going population. The authors develop models for children aged 10 and younger and for all subjects. Despite the article's title, the results do not necessarily support an adjustment of the criteria to protect children. The results instead suggest that, at densities below 27 *Enterococcus* quantitative polymerase chain reaction cell equivalents per

100 mL, young children are less susceptible than the general population.

Another key issue is whether data exist to establish an illness rate threshold differing from that of current criteria. The assumed acceptable freshwater swimming-associated gastrointestinal (GI) illness rate is 8 cases per 1000 swimmers.³ The authors' equations suggest that young children are not more sensitive than all swimmers until the swimming-associated GI illness rate exceeds 22 cases per 1000 swimmers.

The authors note that health assessments were similar to previous studies, but differences in definitions of illness and swimming make it difficult to compare the epidemiological studies with each other and the reported study results with existing EPA criteria. EPA previously defined "highly credible" GI illness as (1) vomiting, (2) diarrhea with fever or a disabling condition, or (3) stomachache or nausea accompanied by fever. The authors' definition of GI illness does not include fever because GI illnesses can occur without fever. However, by broadening the health-effect definitions, the authors invite misinterpretation of the symptoms reported by the participants. The authors also define "swimmers" differently, ie, as those who report immersing their bodies to their waists or higher. EPA previously defined swimmers as bathers who immersed their heads in the water.

A conclusion that the sensitivity of children warrants adjustment of recreational water quality criteria is premature. The results instead highlight the need both for further research and for public and stakeholder-inclusive policy discussions regarding acceptable swimming-associated illness rates. Additionally, these discussions should be informed by independent analyses of the data that are the basis of the research presented.

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The authors respond:

We disagree with Keith Linn's interpretation of our paper, "High Sensitivity of Children to Swimming-Associated Gastrointestinal Illness."¹ His comments are focused on hypothetical interpretation of our results as related to criteria development, rather than the science presented.

Linn notes our definitions for gastrointestinal (GI) illness and swimming differ from those used previously.^{2,3} We clearly justify our rationale for both definitions, and we reject the implication that it is misleading to revisit these definitions, previously used in studies done over 20 years ago.

We make no attempt, as Linn implies, to establish an "illness rate threshold" for comparison with current criteria. We explicitly do not make such comparisons because there are substantial differences between our study and previous studies.^{2,3} These differences include the follow-up period, statistical methodology, and definitions of illness, as well as the indicators and methods used. These differences make simplistic, direct comparisons among studies problematic, and Linn's attempts at such direct comparisons are not justified.

The enhanced sensitivity among children is clearly presented. By highlighting a small range of data, Linn ignores the overall effect. As Linn points out, the difference between swimming and nonswimming children is less than that between all swimmers and nonswimmers in water of good microbial quality as measured by *Enterococcus* quantitative polymerase chain reaction

cell equivalents (QPCR CE), reflecting baseline characteristics and differences between swimming and nonswimming children. This says nothing of the susceptibility of children to GI illness associated with swimming in water of poor microbial quality. With increasing exposure to *Enterococcus* QPCR CE, the risk of illness among swimmers who are children increases at a greater rate compared with other age groups. The odds of illness among children increased 69% with every log increase in *Enterococcus* QPCR CE exposure, whereas the odds of illness among those aged 11–54 years and those 55 years and older increased 13% and 21%, respectively (Table 5¹).

We do not suggest that "the sensitivity of children warrants adjustment of recreational water quality criteria." Our conclusion was limited to the study itself and was presented in the following discussion:

"children up to age 10 years were especially susceptible to GI illness following swimming exposure . . . this is the first study to demonstrate this sensitivity as a function of microbial water quality."

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