From FABIO PARAZZINI,* ALLAN HILDESHEIM,** MONICA FERRARONI,† CARLO LA VECCHIA*‡ AND LOUISE BRINTON*

Sir—We thank Gefeller and Windeler for their careful review[1] of our article on relative and attributable risk for cervical cancer in the US and Italy,[2] and welcome the opportunity to address some of the main issues they raise.

Gefeller and Windeler criticize the lack of precise definitions for the variables used in calculating attributable risk (AR) estimates and the use of the AR rather than the preventive fraction (PF) to estimate the impact of screening on the incidence of cervical cancer. We agree that it is important to define the exposures for which ARs were estimated. It is particularly important that the baseline, or unexposed, level be defined given the sensitivity of the AR estimates to such a choice. For all exposures examined, with the exception of Pap smear screening, the exposures used in calculating AR estimates were identical to the variables defined in Tables 2 and 3. For Pap smear screening, we collapsed 'number of Pap smears' and 'time since last Pap smear' from Table 4 into one AR estimate. Thus, the baseline level for the variable 'inadequate Pap screening' in Table 5 is three or more Pap smears in the past 10 years and less than 2 years since the last Pap smear (excluding diagnostic Paps for cases).

With respect to Gefeller and Windeler's comment that PF rather than AR estimates should be used for screening, we have opted to utilize the AR to estimate the effect of screening. This was done for consistency, since the AR is used for the remaining exposures presented in the table. We believe that this should not hamper the readers' interpretation of the results since, as conceded by Gefeller and Windeler, the PF and AR are highly related measures.

Gefeller and Windeler suggest that 95% confidence intervals around the AR estimates would assist readers in interpreting the findings presented in our article. To this end, they refer us to an article by Greenland.[3] The method described by Greenland, however, applies only to dichotomous variables and all but one of the variables used in our analysis were polychotomous. More relevant to the aims of our study is a recent report by Benichou and Gail[4] which describes the theory for calculating the variance for the AR estimates computed using Bruzzi's method.[5] Benichou and Gail mention that they are in the process of developing a computer program to implement these methods. We agree with Gefeller and Windeler that future studies which utilize AR estimates should attempt to incorporate a method of variance estimation.

Gefeller and Windeler criticize our interpretation of the findings presented in Table 5. They suggest that our discussion is overly optimistic in assuming that 90–95% of cervical cancer is explained by the factors examined and that lack of screening accounts for as much as 45% of invasive cervical cancer cases in the US and 85% in Italy. As we previously discussed in the methods section of our paper, we agree that AR estimates are not additive. However, recognizing the limitations of AR estimates,[6,7] we chose to present the AR statistic to highlight the potential importance of screening in preventing invasive cervical cancer. Despite the higher prevalence in the US of exposure to the risk factors examined, the rate of cervical cancer is higher in Italy. Our use of the AR was an attempt to emphasize the potentially important role Pap smear screening can play in reducing the incidence of cervical cancer. Perhaps we should have been more careful in stating that the risk factors examined explain *in part* 90–95% of invasive cervical cancers diagnosed in the US and Italy, implying that removal of all five risk factors examined and implementation of screening would not necessarily reduce the incidence of invasive cervical cancer by this amount. Similarly, we might have stated that 45% of invasive cervical cancer in the US and 85% in Italy is attributable, *in part*, to inadequate screening practices.

Gefeller and Windeler also criticize the use of case-control studies in evaluating screening programmes. Although it is true that a randomized prospective trial has intuitive appeal, its use to evaluate cervical cancer screening would be unethical. Non-experimental approaches must therefore be utilized to evaluate the efficacy of Pap smear screening. We do not feel that a detailed discussion of the advantages and limitations of utilizing case-control studies to evaluate screening programmes is warranted, given the wide amount of literature already available on this subject. We direct Gefeller and Windeler as well as other interested readers to reviews by Sasco *et al*,[8] Morrison,[9] and Cole

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and Morrison.[10] To quote from Sasco *et al*, 'The typical situation where a case-control evaluation of screening might be the method of choice is when a large number of screening tests have been performed over a period of years, or even decades, but no proper controlled evaluation has been undertaken. Cancer of the cervix is one obvious example. . . .'

Finally, we would like to note a few comments made by Gefeller and Windeler which might be misinterpreted by readers. First, Gefeller and Windeler imply that lead time bias would result in an overly optimistic estimate of the benefit of screening measures. If anything, lead time bias tends to underestimate the benefit of screening programmes by including as cases individuals who were screen-detected.[9] Second, Gefeller and Windeler imply that AR estimates should be used only for causal factors. Although this is generally the case, we believe that AR estimates are useful in interpreting the effectiveness of Pap smear screening in preventing invasive cancer, despite the lack of a causal relationship between screening and cervical cancer. Third, Gefeller and Windeler imply that confounding could account for our finding of a protective effect of screening. Although residual confounding is always a possibility in any observational study, we would like to point out that the risk estimates used in obtaining ARs were adjusted for potential confounding by several factors. Notably, our estimate of risk associated with lack of screening was controlled for potential confounding by age, education, parity, number of sexual partners, age at first intercourse, oral contraceptive use, and smoking.

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Validity of Case-Control Studies and Randomized Controlled Trials of Screening.

From ANNIE J SASCO*

Sir—More and more often in epidemiological literature, we come across papers and comments emphasizing the notion that case-control studies of screening are biased.[1] This statement usually derives from the comparison of results of case-control studies with those of randomized controlled trials (RCT). My contention is that a direct comparison is not meaningful and should not be attempted. In my opinion, it is of the utmost importance to keep in mind that these two types of study measure a different effect.

RCT of screening measure the incidence rate of disease or the mortality rate in two groups of subjects, one having been randomly allocated to a screening programme and the other not. We therefore have absolute rates of occurrence for the two groups and we can compare them by means of a difference or a ratio of incidence or mortality rates. In the context of RCT, everyone in the group randomized to screening has been offered screening, whereas those in the control group have not. Of course, some of the members of the screening group may refuse to be screened, thereby

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