# Sources of error - Assignment solutions

1.

a. $$OR_{HCC/LCC} = \frac{ad}{bc} = \frac{(182)(324)}{(289)(103)} = 1.98$$

$$OR_{LCC/VLCC} = \frac{(289)(45)}{(20)(324)} = 2.01$$

b. The percentages indicate the proportion of individuals within each exposure category (i.e., wiring configuration) who were cases. These percentages do not represent incidences (though Rothman and Greenland call them "pseudo-incidence rates". To calculate incidence one must know the size of the population at risk. The controls here are at best a (very small) sample of the population at risk. The percentages do suggest a dose response relationship, for although the total number of controls was arbitrary and fixed, their distribution among the various exposure categories was not.

c. Potential Sources of Biases.

i) Misclassification of exposure. The measurement of exposure was extremely imprecise. Magnetic fields in the living space were not measured directly. The child's address at death did not necessarily represent where he had lived during the majority of his life (and thus the exposure he had received). Also, wiring configurations could have changed between the time of actual exposure and the time of measurement. Similarly, no note was taken of exposures received when not at home (for instance at school). Assuming that in-home exposure measurement was not feasible, misclassification of exposure could have been reduced if the study had been limited to participants who had the same birth and death address and to those participants who lived in multiple dwellings, all of which were evaluated and had the same "current expected" classification.

ii) Specification of the outcome variable was imprecise. "All cancers" is a very heterogenous group (with more than 1 etiology) rendering the results suspect. The study apparently relied on cause of death from death certificates, without obtaining supporting evidence from medical records and pathological reports.

iii) Only children who had died as a result of their cancer were included in the study. It may be that HCCs are not carcinogenic, but rather are somehow related to prognosis once the cancer has developed.

d. The purpose of selecting controls by taking the next birth certificate was to match on age and to select controls who would have had similar environmental exposures other than magnetic fields. Also, the use of a systematic procedure avoids unwanted variability that creates opportunities for introducing bias.

e. Let: I = overall incidence

$I_1$ = incidence in the exposed

$P_1$ = proportion of population exposed

$I_0$ = incidence in the nonexposed

$R_0$ = proportion of the population nonexposed

RR = relative risk

We know that:

$I = I_1P_1 + I_0P_0$

$I_e = (RR)(I_0)$, so that

$I = (RR)(I_0)(P_1) + I_0P_0$, and

$$I_0 = \frac{I}{(RR)(P_1) + P_0}$$

From the problem,

$I = .001$

$P_1 = .2$; $P_0 = .8$

RR = 2.11 (combining LCC & VLCC into 1 group)

$$I_0 = \frac{0.001}{2.11(.2)+.8} = 0.0008$$

$$\text{Population Attributable Risk \%} = \frac{I - I_0}{I} = \frac{0.001\text{-}0.0008}{0.001} = 20\%$$

(For a review of the 20 years of epidemiologic studies stimulated by this one, see Greenland S, Sheppard AR, Kaune WT, Poole C, Kelsh MA. A pooled analysis of magnetic fields, wire codes, and childhood leukemia. *Epidemiology* 2000;11:624-634.)

2.

a. Study design - a case control study with prevalent cases.

b. Selection bias:

i) Non-response--about 29% of the sample did not return completed questionnaires. If nonrespondents were disproportionately distributed so that the nonresponse rates among MI nonusers of OCs or non-MI users of OC were higher than the other non-response rates, then the odds ratio would overstate the true association.

ii) Selective survival--if OC users and nonusers had different fatality rates from MI, then the prevalent (surviving) MI subjects would not provide an accurate estimate of OC use among women who later develop MI. If the fatal MI rate is higher among nonusers of OC, then the odds ratio observed would overstate the true association.

c. Misclassification of the outcome measure is likely, since:

i) MI may go undetected ("silent MI")

ii) MI may not be diagnosed, despite symptoms (due to, for example, lack of sensitivity of diagnostic tests used)

iii) MI history may be "denied" or mistaken, though for nurses one expects greater accuracy of reporting. No check of hospital records appears to have been made. Probably the true prevalence will be understated.

Misclassification of the exposure measure is also likely, particularly concerning time periods and duration of OC use. Memory in this case is unverified by pharmacy or physician records. Furthermore, the differences among types of OC preparations have not been noted.

The above limitations do not by any means invalidate the study, nor should the investigators necessarily have attempted to collect additional data. But it is important to be aware of the limitations in interpreting the data and in reconciling results with other investigations.

3.

a. Detection bias, in the sense in which Horwitz and Feinstein have applied the term to studies of endometrial cancer and exogenous estrogen, refers to a distortion in the observed proportion of estrogen users among women diagnosed as having endometrial cancer. The distortion in the case would result from the allegedly greater likelihood of diagnostic testing for endometrial cancer in women who take estrogens. The series of events envisioned is: women who take estrogen tend to have vaginal bleeding, prompting them to see their doctor, who then performs a diagnostic procedure (dilitation and curretage ["D&C"]). If an asymptomatic cancer is present, it will come to medical attention. A similar cancer present in a woman not receiving estrogens would go undetected. So the additional diagnostic attention given to the women taking estrogens leads, according to Horwitz and Feinstein, to additional detection of asymptomatic cancers. The end result is that in any series of endometrial cancer cases, the proportion of estrogen users is artificially inflated.

b. "Detection bias", as described above, would tend to overstate a truly positive association between estrogen use and endometrial cancer, because by artificially inflating the proportion of estrogen users among endometrial cancer cases, the difference between cases and controls would become more marked.

c. "Detection bias". in the above sense, is a form of selection bias, since it deals with the selection or ascertainment of cases into the study population. It is true that there is a form of misclassification at work, in that women with asymptomatic endometrial cancer are going unrecognized as cases – and one or two of them might conceivably appear among the control group of a study population. Processes that influence who becomes part of the study population lie in the realm of selection bias. The misclassification of a possible control or two in a study population could cause information bias, but only to a trivial degree. So it

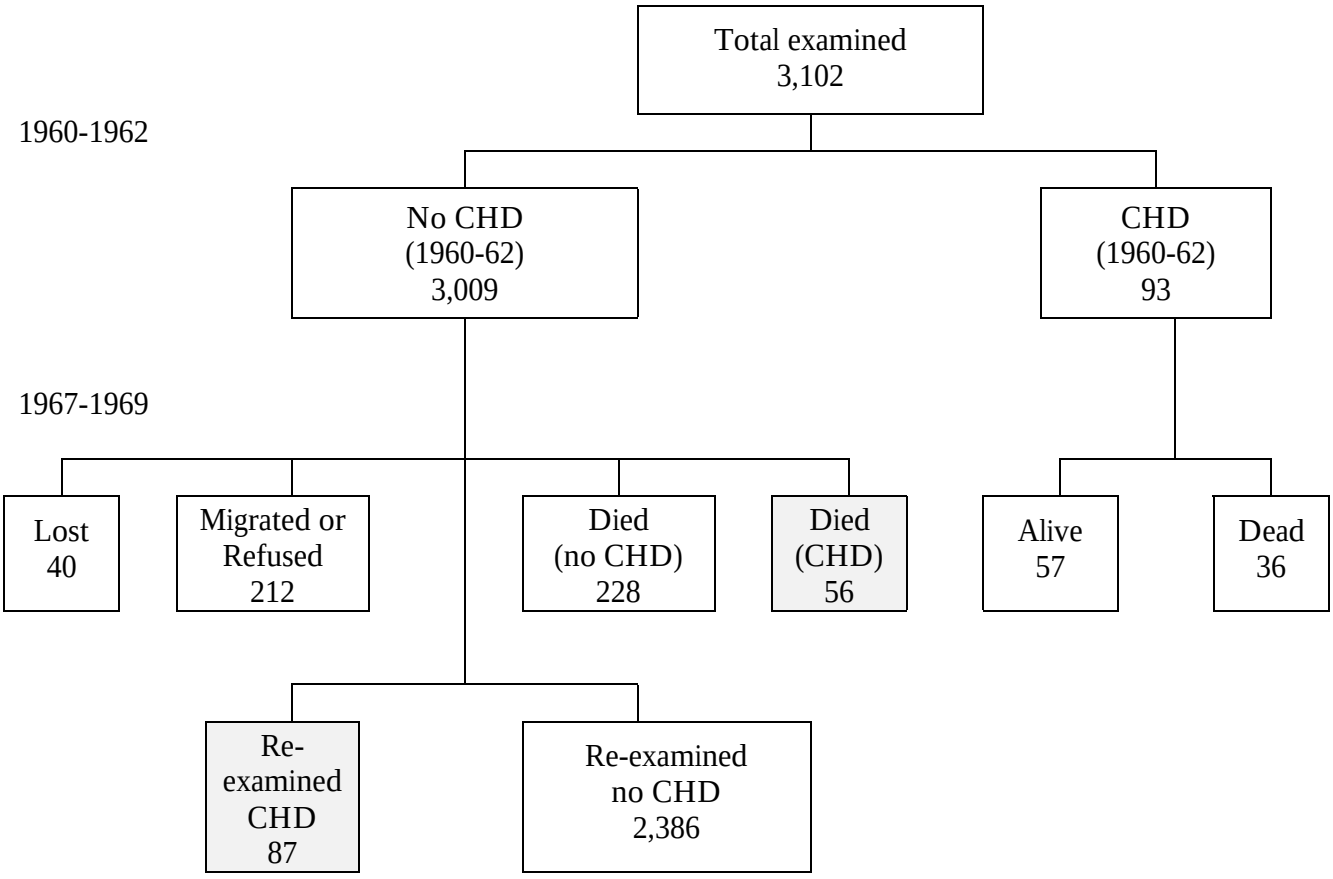
makes most sense to view detection bias as a form of selection bias resulting from over representation of estrogen users among the cases.

d. Detection bias, as described by Horwitz and Feinstein for this situation, is characterized by alpha greater than beta: the probability of coming to medical attention, therefore of being available for the case group of a study, is greater for women using estrogen than for women not using estrogen.

e. The approach adopted by Horwitz and Feinstein attempts to introduce a compensatory distortion in the control group, by recruiting controls from a population that is known to have higher estrogen usage. They therefore seek to increase gamma relative to delta, to increase the proportion of estrogen users among controls. Unfortunately, there is no way to know how great is the distortion of alpha relative to beta, nor to know how much distortion is being introduced to "compensate." Two biases don't necessarily make a right!

f. A presumably preferable alternative, theoretically, would be to increase beta so that it equals alpha, i.e., to introduce some measure to detect asymptomatic cancers in nonusers of estrogen (or in all women, without regard to estrogen use). With present technology, this would require subjecting asymptomatic women to D&C's, an impractical and ethically dubious approach given the low prevalence of endometrial cancer, the nature of a D&C, and the curability of symptomatic endometrial cancer.

a. Flow diagram:




b. Observed cumulative incidence (removing from the denominator subjects lost to follow-up or dying free from CHD):

$$CI = \frac{87 + 56}{87 + 56 + 2{,}386} = \frac{143}{2{,}529} = 0.0565 = 56.5 \text{ per } 1{,}000$$

c. Assume that (1) achieved sensitivity and specificity were, respectively, 70% and 98% for CHD detection among the 2,473 (2,386 + 87) persons free of CHD in 1960-62 who were re-examined in 1967 and (2) there was 100% for both sensitivity and specificity for CHD detection at death).

Since we are assuming 100% sensitivity and specificity for the 56 CHD deaths we will remove them from the following computations.

Let T = "true" nonfatal incident cases

Persons counted as nonfatal incident cases are "true" cases correctly classified PLUS "true" *non*cases *in*correctly classified (see table on next page):

Correctly classified true cases + Incorrectly classified true noncases = Total observed "cases"

$$\text{Sensitivity} \times \text{cases} + (1 - \text{Specificity}) \times \text{noncases} = 87 \text{ observed cases}$$

$$(Se) \times T + (1 - Sp) \times (2473 - T) = 87 \text{ observed cases}$$

$$0.7 \times T + (1 - 0.98) \times (2473 - T) = 87 \text{ observed cases}$$

$$0.7 \times T + 0.02 \times (2473 - T) = 87 \text{ observed cases}$$

$$0.68 \times T + 49.46 = 87 \text{ observed cases}$$

$$T = 55 \text{ "true" nonfatal incident cases}$$

To obtain <u>total</u> new incident cases we add the new cases to the CHD deaths (assumed classified correctly):

$$55 + \text{CHD deaths} = 55 + 56 = 111 \text{ new cases}$$

and substitute the new number into the computation in part b, above:

$$87\text{-month CI} = \frac{111}{2{,}529} = 0.022 = 22 \text{ per } 1{,}000$$

The above computations can be summarized in the following table, which compares the true diagnosis to the study diagnosis assuming 70% sensitivity and 98% specificity for participants who were re-examined in 1967. For example, the upper left-hand cell has the number of persons with CHD (T) who were counted as such:

| | | "True" diagnosis | | |
|---|---|---|---|---|
| | | CHD | $\overline{\text{CHD}}$ | Total |
| Study diagnosis | CHD | $(Se) \times T$<br>$(0.70) \times T$ | $(1 - Sp) \times (2{,}473 - T)$<br>$(0.02) \times (2{,}473 - T)$ | 87 |
| | $\overline{\text{CHD}}$ | $(1 - Se) \times T$<br>$(1 - 0.70) \times T$ | $Sp \times (2{,}473 - T)$<br>$(0.98) \times (2{,}473 - T)$ | 2,386 |
| | Total | T | $(2{,}473 - T)$ | 2,473* |

Given: Se = 0.70, Sp = 0.98

* (Only survivors were re-examined.)

d. The lowest that specificity **in 1960-62** could have been given these data can be found by supposing that all prevalent cases were false positives. In that worst case scenario, the following relationships would hold:

$Se \times T + (1 - Sp) \times (3{,}102 - T) = 93$ observed cases in 1960-62

If there were no true cases, then $T = 0$, $(1 - Sp) \times (3102) = 93$, and $Sp = 0.97$

So the examination procedures in 1960-62 must have achieved at least 97% specificity.