Validity in epidemiology practical

Wellcome Trust Advanced Course – September 2013 – Entebbe, Uganda.

This exercise is based on a series of articles. Please read the extracts then answer the questions given below. The questions relating to each extract have been numbered and refer to the paragraph labelled with the same number.

Extract A. Oral contraceptive use and risk of invasive cervical cancer

Brinton L, Reeves WC, Brenes MM, Herrero R, de Britton RC, Gaitan E, Tenorio F, Garcia M, and Rawls WE.
International Journal of Epidemiology (1990) 19:4-11

A case-control study of 759 invasive cervical cancer patients and 1430 controls in Panama, Costa Rica, Colombia and Mexico enabled an evaluation of risk in relation to oral contraceptive use. Overall use was associated with a 21% non-significant elevation in risk, with some further increases in risk for more extensive durations of use. Although risks were similar for recent and non-recent users (RRs =1.3 versus 1.2), recent long-term users were at highest risk (RR for 5+ years use =1.7, 95% CI 1.1-2.6). Relationships were similar for women with and without a recent Pap smear, arguing against detection bias.. There was little evidence that other risk factors, including smoking and detection of human papillomaviruses (HPV), altered the effects of oral contraceptives. The risk associated with oral contraceptives was significantly increased for adenocarcinomas (RR = 2.2), whereas for squamous cell tumours the effect was minimal (RR =1.1). These results provide some support for an adverse effect of oral contraceptives on cervical cancer risk, although possibly limited only to a subpopulation of cases.

Initial studies examining the relationship of oral contraceptive use to cervical cancer risk were reassuring, but recent investigations have raised concern, particularly for long-term users. Issues of study design and analysis, however, are complex, with questions arising about the potential for confounding, particularly by sexual behaviour, as well as other sources of bias.

Three prospective studies recently reported trends of increasing cervical cancer incidence with extended durations of pill usage. In one investigation, the incidence of cervical cancer after ten years of use was more than four times that in non-users. Although this study had more information on risk factors than many other studies, questions remain regarding the possibility of residual confounding. Thus, a number of case-control studies that have found persistent effects of pill usage after extensive control for a variety of risk factors are noteworthy. In most studies, Pap smear screening appeared to be a more important confounder than sexual behaviour but even after adjustment relative risks of 1.5-1.9 persisted for users of five or more years. Despite these positive findings, the relationship of oral contraceptives to risk of cervical cancer remains unresolved, with several studies concluding that a true causal effect is unlikely.

We had the opportunity to evaluate the relationship of oral contraceptives to invasive cervical cancer in a large case-control study conducted in four Latin American countries. Unique qualities of this study as compared with previous investigations included an extremely high response rate, a large proportion of subjects with only one lifetime sexual partner, information on the behaviour of the male partners of these women, and DNA hybridization assays to detect the proposed aetiological agents for cervical cancer, genital human papillomaviruses (HPV).

METHODS

The case-control study included four study sites: Panama; Costa Rica; Bogota, Colombia and Mexico City, Mexico. Cases consisted of women newly diagnosed with invasive cervical cancer during the period 1 January 1986 to 30 June 1987 at the participating study hospitals. Cases were restricted to women who had not received prior cancer treatment, who were younger than 70 years, and who had been residents of the defined study areas for at least six months. The hospitals included: (1) the National Oncology Institute in Panama, which treats at least 90% of cervical cancer diagnosed in Panama; (2) three social security hospitals in San Jose, Costa Rica, the major

referral centres for all neoplastic diseases in the country; (3) the Ministry of Health Cancer Referral Centre in Bogota, which treats most lower and lower-middle class cancer patients in that city; and (4) the Social Security Oncology Hospital in Mexico City which provides care for the majority of the city's salaried employees.

For each case, two age-matched (by five year groups) female controls were randomly selected. In Panama and Costa Rica, where it was possible to identify a population control series, one community and one hospital control were selected, while in Bogota and Mexico both controls were derived from hospitals.[1]

Hospital controls were selected in Panama and Costa Rica from inpatient services of the patient's referral hospital; in Bogota from eight tertiary level government hospitals, and in Mexico from three social security hospitals serving the population from which cases derived.[2]

Hospital controls were randomly selected from women admitted with non-gynaecological conditions. Women who had a previous diagnosis of cancer, had undergone hysterectomy, or were admitted with endocrine or smoking-related diseases were not eligible as controls.[3a]

Community controls from Panama and Costa Rica were randomly selected from computerised census listings, which are updated every several years. An age-matched control was selected from a random censal segment in the case's county of residence.

A short questionnaire was administered to all selected subjects and those found to have had a hysterectomy were replaced with another randomly selected woman.[3b]

Of the 766 patients and 1532 controls eligible for study, 759 (99.1%) and 1467 (95.8%) agreed to be interviewed. Non-response was accounted for by refusal (0 cases versus 41 controls), death (3 versus 0), language problems (2 versus 10), incompetency (1 versus 8), and inability to locate (1 versus 6).

Interviews were conducted by standardly trained personnel in private settings, either in the hospital or at the subject's home. Information on sociodemographic factors, residential patterns, living conditions, pregnancy history, hygiene and menstrual factors, sexual behaviour, contraceptive and medical history, smoking, diet, marital and occupational factors, and family history was ascertained. Oral contraceptive information included years of usage for each episode of use, but no attempts were made to collect details on specific brands. Interviews lasted an average of 60 minutes.

Q1. Suggest reasons why 'a population control series' was identified for Panama and Costa Rica but not for Bogota and Mexico.

Q2. Given that the authors would regard 'a population control series' as being less likely to introduce selection bias than using hospital controls, why do you think that for Panama and Costa Rica they included a hospital and a community based control for each case?

Q3.(a) Why were women with a previous diagnosis of cancer excluded from the hospital control series?

Q3.(b) Why did the hospital and community controls exclude women who had had a hysterectomy?

Extract B. Evaluation of the protective effect of BCG vaccination by a case-control study in Yaounde, Cameroon

Blin P, Delolme HG, Heyraud JD, Charpak Y, Sentilhes L
Tubercle (1986) 67:283-288

A case-control study carried out in Yaounde (Cameroon) shows that the protective effect of BCG against pulmonary tuberculosis in the young adult was 66% (relative risk 0.34). This result is not affected by taking into account various factors such as sex, age, socio-economic class and geographical origin.

MATERIALS AND METHODS

The cases were recruited between September 1983 and September 1984 at the only tuberculosis dispensary of Yaounde, which is the centre for suspected tuberculosis patients from the capital and its bordering departments. All patients attending this centre had a chest X-ray and microscopic examination of the sputum. In the case of patients with X-ray lesions, the sputum examination was repeated three times.

All patients with sputum positive pulmonary tuberculosis (Ziehi-Neelson staining technique and double reading of the plates) were included in the study: age range 17-26 years, and of Cameroonian nationality. As bacillary pulmonary tuberculosis is rarely diagnosed in children under 17 years in Yaounde these were not included.

During the mass vaccination campaigns, BCG was administered without prior tuberculin testing and therefore some tuberculin positive subjects were vaccinated. The subjects included in this study were from 0-18 years during the mass vaccination campaign. According to the tuberculin surveys carried out in Yaounde, less than 25% of these subjects should be tuberculin-positive.[6]

The tuberculosis dispensary of Yaounde has a large geographical recruitment, and we chose three centers to find controls: the antivenereal dispensary of Yaounde and the general dispensaries of Bafia and Ebolowa, two towns in the region from which cases were recruited. The controls has no history of tuberculosis nor any symptoms suggestive of tuberculosis (cough and expectoration, haemoptysis, prolonged fever or loss of weight). They were aged from 17-26 years, of both sexes and of Cameroonian nationality. From September 1983 to September 1984 regular visits were organized at these centers to find controls. At the times of these visits all the patients were seen by two doctors from OCEAC who selected them according to the inclusion criteria.[5]

Evaluation of the vaccination

Patient's recall of BCG vaccination was too imprecise to be reliable and there were no existing records on vaccinations. However, vaccination status can be estimated objectively from the residual scar: after BCG vaccination, subjects with black skin frequently develop an identifiable keloid scar. Consequently, the anterior part of both forearms was examined, which was the site for BCG vaccination during the mass vaccination campaigns (the upper part of the arm being reserved for smallpox vaccination). We considered as unvaccinated those who did not have a BCG scar as the proportion of vaccinated subjects who did not develop a scar is low (2.5%) when the injection has been carried out correctly.[4]

Q4. What assumptions are made in the way that BCG vaccination status has been measured?

Q5. Discuss the ways in which the sources of controls may have led to selection bias.

Q6. To what extent will the results by biased by the fact that some of the subjects were vaccinated when they were tuberculin positive?

Extract C. Dietary fat and risk of breast cancer

Van't Veer P, Kok FJ, Brants HAM, Ockhuizen T, Sturmans F, Hermus RJJ
International Journal of Epidemiology (1990) 19:12-16

Age-adjusted dietary fat intake of 133 incident Dutch breast cancer cases was significantly ($p<0.01$) higher than in 289 apparently healthy controls (mean and standard deviation; 102±36 g and 92±30 g, respectively). The age-adjusted relative odds of breast cancer showed a positive trend ($p<0.05$) with increasing fat intake. The multivariate adjusted relative odds was 3.5 (95% CI =1.6-7.6) for subjects in the highest quintile of fat intake (above 113g) compared to those in the lowest quintile (below 65g); this corresponds to a 30% increased risk per 10% of energy derived from fat. The association could not be attributed to energy intake, nor to the degree of saturation of the fat nor to any specific dietary source of fat.

The impact of diet on breast cancer prevention may be of great importance, especially in Western countries, where the incidence is high and stage-specific survival does not improve. Cross-sectional data and animal experiments point at either energy or fat intake as risk factors. The role of energy intake also hampers the interpretation of epidemiological studies. Case-control and cohort studies generally have failed to contribute convincing evidence with regard to the fat hypothesis, because their interpretation was hindered by methodological problems in dietary assessment or selection of the control group. In the Netherlands, known for both a high breast cancer incidence and mortality, as well as a high per capita fat intake, we conducted a casecontrol study on dietary fat intake and breast cancer and applied an extensively standardized and reproducible dietary history technique for the assessment of usual fat intake.

SUBJECTS AND METHODS

Study population

The study was conducted in 1985-1987 among Dutch Caucasian women aged 25-44 and 55-64 years, residing in a defined region of the Netherlands. A total of 168 newly diagnosed breast cancer cases from 17 hospitals in the study region were enrolled in the study, either by cooperating surgeons or by regional cancer registries. The diagnosis was histologically confirmed in 96%> of the cases. Of eligible cases 134 (80%) agreed to participate in the study.

An age-stratified sample of controls (548 women) was obtained from the municipal population registry in the same area as the hospitals.[7]

After exclusion of 19 subjects who did not fulfil the eligibility criteria (n=8), or who could not be traced (n=11), a total of 289 (55%) eligible control subjects participated, with age distribution and period of investigation similar to the case series.

In order to evaluate representativeness of the control group, the entire control sample was asked to complete a condensed postal questionnaire. This questionnaire was returned by virtually all participating controls and by 89 (37%) of the non-participating controls. No major differences were detected between participants and non-participating controls with regard to age, age at first full-term pregnancy, parity, weight, height and body mass index. With respect to food consumption, no differences were observed in daily intake of fat containing foods (fat-content of milk products; meat products and cheese versus sweet food items on bread), bread, eggs, and fish. The former, however, tended to use wholemeal bread more frequently.[8]

Q7. What assumption would you have to make before accepting that the use of population controls was appropriate?

Q8. Does the fact that there were few differences found between 'participating' and 'non-participating controls' help you assess whether selection bias might be a problem in this study?

Extract D. Efficacy of BCG in Papua New Guinea

Murtagh, K
Letter, *Lancet*, February 23, 198

Sir-Your January 12 editorial discusses experience in India with BCG. When working in Papua New Guinea I found it depressing that so many children with tuberculosis had had BCG, and there was much debate as to whether the BCG vaccination was giving any protection.

Between May 1975 and June 1978, more than 400 children in Port Moseby and the surrounding central province were put on anti-tuberculosis therapy. 131 children had the diagnosis confirmed by the isolation of *Mycobacterium tuberculosis* from gastric aspirate, sputum, discharging sinus swabs, pleural aspirate, ear swab, or CSF, and in a further 33 children the diagnosis was confirmed by a glad biopsy showing the typical histology of active tuberculosis lymphadenitis. Of these 164 children, in whom the diagnosis was considered proven, 114 had the presence or absence of a BCG scar recorded. The scar was present in 84 (73.7%) of the 114 children, and vaccination was further confirmed by health records in 36 of these 84 children. In the children with military or meningeal tuberculosis the percentage who had had BCG was slightly less – namely, 10 (59%) of the 17 children with military TB and 10 (67%) of the 15 with meningeal tuberculosis. It was difficult to assess how many children in the general population had received BCG as there were many people living in remote villages. During the period July 1977 to June 1978, 121 children admitted to the surgical section of the children's ward were examined for a BCG scar. 100 (78%) had evidence of a vaccination. **9 & 11**

BCG is given routinely in Papua New Guinea in the neo-natal period and children are revaccinated on entering school.

It was felt that these figures indicated that the vaccination was probably giving some protection but that even more effort should be placed on the tracing and treating sputum positive adults if there has to be any hope of preventing the disease in children and that improving their nutritional status would also help in reducing the morbidity and mortality. [10]

Q9. Is the study described in the letter a case-control study?

Q10. On what basis does the letter writer conclude that vaccination 'was probably giving some protection'?

Q11. What reservations have you about this conclusion?

Extract E.

Cocaine abuse and congenital syphilis
(Based on Webber MP et al, 1993)

Infants born to mothers with syphilis infection may themselves be infected at birth. Syphilis detected early in pregnancy is easy to treat, whereas the effects of congenital syphilis are not. The following comes from a report of a case-control study of maternal risk factors for congenital syphilis in New York City:

> "After decades of quiescence, congenital syphilis re-emerged in the 1980s as an epidemic disease among poor, inner-city infants. In New York City, for example, the number of reported cases rose from 26 in 1980 to more than 1000 in 1989, despite only a modest increase in the number of live births. Several studies have associated maternal cocaine use with the increased incidence of congenital syphilis."

Consistent with earlier studies, the New York case-control study estimated that a history of maternal cocaine use increased the risk

of congenital syphilis by a factor of nine (odds ratio = 9.1, 95% CI 4.7-29.2).

Q12. How would you explain this finding?

Having adjusted for ethnicity and whether each mother has used the prenatal care services, the odds ratio for cocaine use was estimated as 4.87 (95% CI 1.82-13.04). The effect of prenatal care use (yes/no) on the risk of congenital syphilis, adjusted for cocaine use and ethnicity, was strong (odds ratio = 11.03, 95% CI 1.31-93.09).

Q13. How do these results help you draw conclusions about the association between maternal cocaine use and congenital syphilis?

Extract F.

Suicide rate, prevalence of diagnosed depression and prevalence of working physicians in Hungary
(Based on Rihmer z et al, 1993)

The table below is from a paper that investigated the relation between suicide rates in counties of Hungary and the number of working physicians per 100,000 inhabitants.

Table 1: Prevalence of working physicians, prevalence of reported depression and suicide rates per 100,000 population in 16 counties of Hungary in 1986.

Suicide county*	**Prevalence of working physicians in decreasing order**	**Prevalence of reported depression**	**Suicide rate per 100,000 1986**
Zala W	252	20.9	26.9
Vas W	246	24.1	23.7
Gyor-Sopron W	242	14.8	22.7
Veszprém W	238	18.1	35.4
Komárom W	238	17.8	35.2
Tolna W	235	12.5	44.5
Heves E	234	13.0	32.0
Somogy W	226	13.4	41.1
Nógrád E	221	34.6	25.8
Bács-Kiskun E	220	5.4	68.0
Fejér W	209	9.9	43.2
Szollnok E	209	8.6	52.1
Borsod-Abaul-Zemplén E	206	6.6	41.8
Békés E	190	5.3	52.8
Pest E	178	9.5	49.1
Szabolcs-Szatmár E	168	6.9	58.4

*W and E indicate whether the given county is located on the western or eastern part of Hungary, using the river Danube as a

cut-off line because it crosses Hungary nearly in the middle from North to South.

The paper concluded that the number of physicians per head of population may be 'one important factor resulting in the regional differences in suicide mortality in Hungary'. The author's conclusion also implies that medical intervention in depression can have a major impact upon suicide rates.

Q14. Examine the data in the above table (you may wish to plot it out on graph paper), and describe what you find.

Q15. Do you agree with the authors' conclusions? What alternative explanations might there be for the associations observed in the table, and what further information might you want before reaching any further conclusions?

Extract G

Obesity and stroke mortality

You have conducted a cohort study and are interested in looking at the relationship between different levels of obesity and stroke mortality. You have also measured the blood pressure of each individual in the study and shown that increased obesity is associated with increased blood pressure and also that blood pressure is strongly related to the incidence of stroke mortality.

Q16. Using just this information, do you think that you should adjust for (stratify by) the levels of blood pressure in the analysis of the effect of obesity on stroke mortality? Think about your answer and the reasons for it before moving on to part Q6.

Q17. You believe that both obesity and blood pressure are risk factors for stroke and that they both operate independently to influence stroke mortality. Should you now adjust for levels of blood pressure in this analysis?

Q18. Another researcher wishes to analyse your data and believes that increased obesity increases blood pressure

which in turn increases mortality. Should this researcher adjust for levels of blood pressure in the analysis of the relationship of obesity to stroke?

References

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