EPI511 extra credit critique paper

"Lifetime cigarette smoke and second-hand smoke and cervical intraepithelial neoplasm – A community-based case-control study”

In design and data collection, Tsai et al.'s research on the causality of smoking, SHS (Second Hand Smoking) and CIN (Cervical intraepithelial Neoplasm), the researchers hypothesized that in recent literature, the relationship of SHS and CIN are not yet conclusive, and with evidence on the importance HPV played in the causation of cervical cancer, the researchers compared both a community-based case control study was conducted to determine the causality of SHS and CIN. The research also wants to compare itself to a previous case-control study similar in nature to this one, which is done by the same group of researchers in a rural county in Taiwan.

In the case-control study, the researchers identified smoking, second hand smoking as the exposure of interest; the status of CIN (I, II and III) are the disease of interest. To determine the association of SHS and CIN in the community, the optimal choice is to conduct a prospective cohort study and trace the exposure (smoking and second-hand smoking status) before onset of disease given the base population eligible for national health insurance covered pap smear screening is all women aged 30 and above in Taiwan. Otherwise, a prospective cohort study is more preferred to prevent loss of follow-up and the selection and information bias that might likely occur as with the case-control study mentioned in this study, especially when it comes to measuring SHS which is not easily quantifiable and not powerful enough to generate substantial conclusions from within a small set of subjects. Therefore, case control design is not the best design, but when funding, resources and time are limited, looking into the screening registry to conduct a case-control is the fastest and less time-consuming design at hand.
The study population is drawn from the 155,630 women aged 20 or over in the Kaohsiung county screening registration, among them 1,463 was screened as having lesions and are referred to follow-up or treatment, follow-ups could be “watch-and-wait” method for women identified with CIN1 or mild dysplasia, or direct treatment like cryotherapy or CONE/LEEP procedures. The final subjects involved in the study were women who opted for a cervical biopsy to determine if they needed further treatment or a “watch-and-wait” follow-up. The comparison group was drawn from the same registry that was screened negative for cervical cancer lesion.

Problems stemmed from with the selection may result in plenty of selection bias as follows: As I am from Taiwan, I am familiar with the health system there. First of all, Pap smear registry in Taiwan are by law only required to keep records of those screened above the age of 30 unless physicians find irregularities in women under 30, so the cases from 20-29 years of age are actually screened involuntarily, meaning most might have a predisposing condition that lead physicians to believe they needed a out-of-pocket pap-smear and report it to the Kaohsiung county health bureau. Meaning 20-29 year-olds in the group are high-risk groups already identified in the registry, this could lead to two consequences, one, a differential bias in cases because perhaps more 20-29 year-olds with high risk, compared to the older population, will be diagnosed with dysplasia or neoplasia, the proportion of age distribution is not shown and even though it is adjusted for, the selection bias can contribute to a non-differential bias in both control and cases, shifting the OR to over-represent cases of cervical neoplasia compared to the general population. Second, if the 20-29 year-olds are coming for regular follow-ups post treatment, which we have no record and cannot tell from the study, they will have regular pap-smears but are HPV positive, this will cause differential bias in the control group, thus trimming down the effect of HPV to cervical neoplasia. Also, screening in Taiwan is not mandatory, therefore those that are more health conscious will be screening more, if not referred by the physician if bleeding or abnormal bleeding were
detected, those that signed the consent form, the 177/1463 women, might be more health conscious. Lastly, nearly 70% of the possible sample population is lost to incorrect contact, were they of a lower SES or of a minority group that lives in unreachable areas? Also, the Kaohsiung country hospital is not restricted to those living within the county, thus to say they selected the county because it is in proximity and similar to Chia-Yi county (the previous study) is not valid, nor is the data generalizable, thus hindering external validity. Of the 10% loss of sample population who preferred another pap-smear or direct treatment, the research lost a population that are either in CINI early phases or late phases of neoplasia, or perhaps non-symptomatic at all, without information of the distribution of severity of diagnosis from this group of women, selection bias is present especially when the researchers grouped inflammation in one group, CINI in one group and CINII or above in another, it might be possible that CIN1 will form the majority of the case while in real life, inflammation is the major cause of abnormal pap smear.

Information bias is also present: misclassification of positive and negative smears is unavoidable due to the limitation of the sensitivity and specificity of Pap smear. The cross-sectional nature of a one-time biopsy exam may detect woman who are at different phases of neoplasia progression, false positives are categorized in the case group (6/177), and as Taiwanese journals have discussed, a larger number of undetected cervical cancer are due to false negatives, which are all categorized into the control group. Smoker and SHS status collection further complicates the situation because of recall bias: those with a positive smear might over-report SHS status, SHS is very hard-to-quantify, smoker status was questionable because it was limited to a randomly testing urines of smoker/SHS/non-smoker due to limited funds when it should be evenly distributed according to case and control population’s smoker/SHS/non-smoker status, over-representation of SHS in urine analysis fails to confirm SHS has a higher cotinine/creatinine level, therefore bias persists regardless whether information on the status about recent exposure to smoke is collected.
In the introduction, the authors failed to explain what confounders they will be controlling for and reasons for controlling them, the only mention was HPV is a major cause of cervical dysplasia. The researchers did not explain reasons to control for these factors, especially when HPV is proven to be a direct causation of cervical cancer; confounding for cooking oil fume exposure is as hard to quantify as SHS and therefore the credibility of such is questionable; also, the nature of HPV transmission as an STD makes family history of cervical cancer no relation to offspring’s chance of getting cervical neoplasia (assuming no sexual relationships are between generations, which is perhaps very uncommon and unable to research via phone survey.), thus it is a waste of time to control for family history. The authors limited diagnosis misclassification by confirming biopsy results with another pathologist after data collection, and calculated a Kappa score to avoid recall bias, but only 100 participants were included in the second survey, a 0.87 Kappa out of 100 indicated that out of 700, there’s at least 100 who misreported their smoker status. A short literature table featuring the association of smoking and cervical neoplasia to support their hypothesis is presented, but confounding for HPV and not calculating its additive effect when the rest of the literature regarding causality of cervical cancer found HPV as a main factor does not make SHS seem any less unimportant.

The authors did not discuss about the sample size and power at all, as mentioned above, only 10% of the possible sample population are recruited successfully, any further analysis would not be justified until sample power is calculated or explained, nor was a sample size proportion calculation inferred. Out of 1463, in a study with smoking/SHS as exposure of interest, less than 70 were smokers, which is 4%, compared to a 10% smoking prevalence among women, the literature the researchers listed supported that 3-4% of women smoke, it is skewed compared to the rest of the literature on female smoking prevalence in Taiwan and intentionally leads readers to believe the small number of smoker is justifiable when in fact they should put more weight on smoker and SHS in the population if they need
accurate results.

In data analysis and results, the researchers tried to minimize confounding by controlling for age, education level, times of prior pap smears, lifetime sexual partners, age of sexual debut and family history of cervical cancer, cooking oil fume exposure and HPV infection. Confounding for HPV will blur the results and hinder interpretation and cause the confounding effect to be a biased to favoring smoking and SHS to be highly associated with neoplasia, and the true association between SHS and neoplasia is greatly exaggerated. The researchers did not define reasons to adjust for the above when some are confounders and some are effect medications that might act as synergistic or antagonistic effects to the association between SHS and neoplasia. It ignored that single most important factor to neoplasia- HPV infection, is the major must-exist component leading to neoplasia, and SHS is a none-necessary component cause, an additive to the disease.

In the analysis, authors did not provide the incidence of overall SHS/smoker prevalence nor screening sensitivity and specificity in the area it conducted research on, the proportion of people who will progress from inflammation towards CIN1 or above was not provided, either. Although the questionnaire is developed to ask about smoker/SHS status, it was not calculated for intra-consistency, interviewers were not shown to be trained prior to phone interviews; although ORs shown smokers/SHS with positive HPV to have a higher OR than none smokers/SHS with positive HPV in terms of neoplasia, it might be generating results that are invalid and unreliable. The researchers failed to use stratified analysis or other methods to determine the nature of other variables as confounders or interactive variables. The use of sequential or simultaneous analysis is also lacking.

To determine causal association of SHS and neoplasia of the cervix, besides the definite causal relationship between HPV infection and cervical cancer, as geneticists would say, we have to always take into consideration the multicausality of the nature that all cancers are genetic diseases, E6, E7 and immune system and lifestyles contribute to the making of cancer
(infectious origin or not); therefore, according to Hill’s suggestion when inspecting for causal association: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy are important. It is plausible to assume that if tobacco consumption can cause the body to increase cotinine/creatinine level and that it is proven to be synergistic with HPV leading to cervical cancer, SHS might do the same; the results would then be coherent with the rest of the research starting from the 80’s when the causal link between HPV and smoking is not yet fully established; although if we test for cooking oil fume exposure, the same conclusions might be drawn, because it contains cotinine/creatinine, too.

The strength of HPV and cervical cancer is so strong in this research, it only exemplifies the fact that SHS may just be one little additive effect leading to cervical cancer, though we cannot refute the idea that smokers have higher folds of risk of getting cervical cancer, in this research, there are no matching process to prove that smokers with a negative smoking status indeed has a higher risk of getting a positive smear result than their non-smoking counterparts. Therefore, SHS is analogically, if we think about the association of SHS with cardiovascular disease, though the association is weak; it is undeniable that SHS does play a role in cancer progression, an exacerbation mayhaps.

In interpretation and discussion sections, I slightly agree with the researchers that SHS does take part in the process of the progression of cervical neoplasia, the researcher has compared past cohort researches of the causal relationship of smoking on cervical cancer to show that theirs was the first to conclude SHS has a causal association to cervical cancer (and not the other way around, certainly), and that this research is important because it objectively verified SHS exposure and also provided information on HPV exposure. It did mention potential biases like misclassification of smoker and nonsmokers and how more misclassification in the smokers category would lead to underestimation of CIN progression contributable to smoking. The second limitation this research justified was the low correlation
between SHS and cotinine/creatinine levels are due to the unavailability of recent tobacco exposure in the provided questionnaires, this elicits doubts towards research, because if low correlation will lead to bias, making additional follow-ups when telephoning the 100 population on reconfirming smoking/SHS exposure status midway in the research wouldn’t seem to be a difficult or financially difficult task. The utmost questionable process the researchers tried to justify, to which the answers I do not agree with, is the small sample size that makes results ungeneralizable, it added a double-blind pathologist report on 50 of the randomly selected biopsy reports to increase validity of the biopsy results, but the unsolvable issue is the screening results of non-participants and the representability of the sample in the county. As mentioned in the critique in the design phase section, biases of this research stems from sampling errors; the large population lost to erroneous contact address/phone number indicates a loss of those of different SES, those who doesn’t have the access to phones; those that live outside the county who infrequently visits; the voluntary screening shows the screened women are potentially more health conscious and assume participating will receive more medical attention, causing both case and controls to have non-differential classification and blur out the association of both HPV infection and SHS status. On the other hand, if we think of it the other way, women might participate because smokers would find a way to justify the reason they got positive smear results, this would cause differential misclassification in the case group, diluting the relationship of HPV and cervical cancer, and exaggerating the relationship of smoking and neoplasia, furthermore, given the nature that women are likely social smokers in Taiwan who doesn’t always regularly smoke, those who are previous light smokers would under-report their smoking status and instead opt to consider themselves as exposed to SHS, thus exaggerating the association of SHS and neoplasia even more.

No matter how “blinded” were the physicians and nurses of the HPV and smoker status throughout the process of biopsy or interview, the researchers will not be able to give more
validity to the research, though reproducible, the results will yield the same interpretation and is weak in association though SHS does take part in the multicausal pathway of progression of cervical neoplasia. The authors were too blunt to state that SHS is another cause of cervical cancer, it is just an additive effect that might contribute to the progression of disease.

The clinical value of the research lies in its multiple errors in the design phase and analysis phase. Kaohsiung county hospital should collaborate with the national cancer registry to match pairs for women of 30 and above and establish a cohort that also registers HPV infection status, onset of neoplasia and the natural prevalence and mortality of disease, and use conditional logistic regression to improve power of interaction between smoking and HPV infection among the randomly chosen population of research, also, HPV viral load and viral type are as important as infection status. The first smear date, first HPV positive status detected as well as years of being a smoker/SHS exposure are also important dates to record so as to identify the timing of smear and causality of HPV and cervical cancer. Elimination of repeated smear results from health-conscious women and those who received treatment and are in follow-ups are essential to keeping the results derived from the research as generalizable as possible.