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Smith, D. R.; Beh, E. J. "Hirayama, passive smoking and lung cancer: 30 years on and the numbers still don't lie" Public Health Vol. 125, Issue 4, p. 179-18124 (2011)

Available from: <http://dx.doi.org/10.1016/j.puhe.2011.02.008>

Accessed from: <http://hdl.handle.net/1959.13/1054176>

Commentary

Hirayama, passive smoking and lung cancer: 30 years on and the numbers still don't lie

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Early 2011 represents the 30th anniversary of a groundbreaking publication on the effects of passive smoking and its relationship with lung cancer. In the modern age it is difficult to remember what things were like thirty years ago, at a time when tobacco use was very common and one could freely light up in restaurants, bars and workplaces – pretty much wherever they wanted. Non-smokers in the vicinity had no choice but to inhale second hand smoke. And there was a lot of it. Depending on the country and demographic, between one-third and one-half of all people used tobacco, including many in the health care professions.¹ Nonetheless, the tide was about to turn as the evidence against passive smoking steadily mounted. Indeed, the possibility that tobacco might harm non-smokers had actually been considered within the scientific community for some time. By the late 1970s for example, Enstrom² had commented on a large relative increase in lung cancer cases among non-smokers in the United States observed between 1914 and 1968.

Things came to a head in January 1981 when Takeshi Hirayama (1923-1995) from the *National Cancer Centre Research Institute* (NCCRI) in Japan published a groundbreaking study in the *British Medical Journal* titled: 'Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan'.³ A flurry of Letters, arguments and criticisms followed Hirayama's publication,⁴⁻⁷ calling into question everything from his sampling technique, to his underlying mathematical assumptions and subsequent statistical analysis. Nevertheless, with clear, rational explanation and adherence to sound statistical principles, Hirayama and others systematically refuted their criticisms.⁸ In the current article we discuss some of the mathematical aspects of Hirayama's study, as well as some of the arguments initially used to challenge his findings. Since many of these criticisms revolved around the

data presented in Table 1 of Hirayama's paper, we shall also base our current examination on these figures.

Hirayama used standardised mortality ratios to examine the effect of passive smoking on lung cancer among a population-based sample of non-smoking women. Since much of his study focussed on the relationship between tobacco consumption among men and whether their spouse subsequently died of lung cancer, it is very important to aggregate the age variable. In the following analysis we shall see why. Firstly, let us consider the following simple summaries. By calculation, we can deduce that the odds of a wife dying from cancer if her husband is a non-smoker = $146 / 100,000$. Similarly, the odds of a wife dying from lung cancer if her husband is a relatively light smoker (either an ex-smoker or consuming 1-19 cigarettes / day) or a relatively heavy smoker (consuming at least 20 cigarettes / day) = 195 and 220 / 100,000, respectively. On the face of it, these figures seem to provide compelling numerical evidence that the odds of dying from lung cancer significantly increase the more one's spouse smokes. However by performing a chi-squared test of independence, a p-value of 0.177 is obtained, which suggests no statistically significant association between passive smoking and lung cancer (at the 5% level of significance). For such a test, the chi-squared statistic is 3.469 and is tested with two degrees of freedom.

While things may not be looking too good for Hirayama's results at this point, suppose we now examine the association between lung cancer and passive smoking for each age category, considering firstly those husbands aged 40-59 years. For this age group, based on the data in Hirayama's Table 1, the odds of a wife dying from

lung cancer given her husband is a non-smoker = $78 / 100,000$. Similarly, for a relatively light smoking husband or a relatively heavy smoker this ratio becomes 130 and $175 / 100,000$; respectively. Again, there appears to be a significantly higher risk of dying from lung cancer the more one is passively exposed to tobacco smoke. However, for the analysis of this particular age group, the p-value = 0.053 – a result that is barely statistically significant at the 5% level. For older husbands (aged at least 60 years) the odds can be calculated as 267, 340 and 410 for every 100,000 people in the sample at each of the three smoking levels. Again, this also suggests a significantly increased risk of dying from lung cancer the more one is passively exposed to tobacco smoke. Interestingly, the p-value when analysing this part of the table (based on the chi-squared test of independence) is only 0.378. Therefore, the risk of dying from lung cancer due to passive smoking appears to be less of an issue for those whose husbands are older. As such, why does there appear to be no statistically significant evidence linking passive tobacco exposure to lung cancer in Hirayama's study? Certainly those who criticised his paper were quick to highlight this point. But Hirayama was correct, and we shall see why.

Firstly, it is important to recognise that any conclusions drawn from the simple chi-squared analyses described above are by definition quite superficial, and therefore, cannot elucidate the full picture. On the other hand, if we consider each of the three variables simultaneously (smoking frequency, cancer status, and husband's age), then the chi-squared statistic becomes a massive 147,520 with a p-value of less than 0.001 (in fact, the p-value for this calculation becomes so small that it actually contains 15 zero's). Such a result concludes that there is indeed some relationship between all three variables. So, how and why do we obtain a statistically significant

association for such a test, when our previous calculation appeared to be inconclusive? The answer is due to a surprisingly common statistical phenomenon known as Simpson's Paradox.

Simpson's Paradox⁹ is a form of statistical confounding that occurs where the introduction of a third factor is seen to reverse the effect of the first.¹⁰ It can occur when the incidence of some particular attribute is being investigated and the population under study is split into parallel subcategories. This may lead to the population with a higher overall incidence actually displaying a lower incidence within each subcategory.¹¹ From a mathematical perspective such a paradox occurs when one falsely aggregates across a confounding variable that establishes the link between the variables of interest. In Hirayama's study for example, it occurs if the variable (husband's age) is ignored and one subsequently concludes that no statistically significant association exists passive smoking and lung cancer. On the other hand, when this variable *is* included in the analysis an association becomes apparent, and closer examine of the chi-squared statistic can reveal its source. This is achieved by calculating the chi-squared statistic for each pair of variables (aggregating over the remaining variable) and including a trivariate association term. Doing so reveals that simply focussing on only the cancer and smoking variables gives a misleading result. Closer examination of all three variables, on the other hand, provides evidence of a clear and very dominant association between all three.

Interestingly, some of Hirayama's critics at the time actually called for more detailed data to be collected and for his analysis to be re-examined. This strategy held some merit as not all population-based studies of the era had conclusively demonstrated

tobacco as a definitive lung cancer risk for non-smokers. In mid-1981 for example, Garfinkel published a study where the number of lung cancer deaths among passive smokers was slightly higher, although the finding was statistically insignificant at the 0.05 level.¹² Nevertheless, as the evidence began to mount, the balance of opinion slowly changed. In the same year as Hirayama's study was published for example, Trichopoulos¹³ reported an increased relative risk for lung cancer of between two and three-fold among non-smoking Greek women whose husbands smoked. Twenty-five years later Wen demonstrated a similar phenomenon in China, including the dangers of passive smoking at work.¹⁴ This latter point is especially important given that, until strict legislations are enforced worldwide, the workplace represents one of the most important sources of environmental tobacco exposure.¹⁵ By the year 2000 a report by the *International Agency for Research on Cancer* (IARC) had conclusively proven the dangers of second hand smoke.¹⁶ It is ironic that the 'additional research' requested by Hirayama's original critics would actually prove that he was correct all along.

For all its breakthrough findings, it is important to consider the man behind the study itself. Takeshi Hirayama, MD, DrMedSc, MPH, was born in Kyoto in January 1923 and spent his high school years in Tokyo before moving to China where his father was Professor of Surgery at the *South Manchuria Medical College* (SMMC).¹⁷ By the 1950s, Hirayama had returned to Kyoto University in Japan, where he graduated with a Doctorate in 1951. Interestingly, his Chinese medical school had played a unique role in Japanese medical research during this period and many of its graduates who entered academia had also matriculated to Kyoto University in a similar manner.¹⁸ The SMMC, which taught its lessons in Japanese,¹⁹ would eventually merge with the Mukden Medical College in 1949 to become the modern day *China Medical*

University - one of the country's premier medical schools to this day.²⁰ In 1952, Hirayama completed a Master of Public Health degree at Johns Hopkins University in the United States, and in 1959 went to New York to study associations between smoking and lung cancer at the Sloan Kettering Memorial Cancer Center.²¹ In 1965 Hirayama was appointed Chief of the Epidemiology Division at the NCCRI in Japan, during which time he initiated and directed a population-based cohort study of approximately 260,000 people in 6 prefectures.²² This project investigated the health effects associated with tobacco smoking, alcohol consumption and dietary habits; initially running for 17 years until Hirayama's official retirement in 1985.

Aside from its groundbreaking elucidation of passive smoking as a risk factor for lung cancer, Hirayama and the cohort study he directed were also instrumental in the understanding of many other important lifestyle factors, such as the role of green-yellow vegetables in reducing cancer risk.²³ In recognition, Hirayama received the Ramazzini Award in 1989 for his contribution to the understanding of lifestyle factors in the genesis of cancer.²⁴ Hirayama also worked with the Indian *National Cancer Registry Programme* (NCRP), with whom he was a WHO consultant from 1982 onwards.²⁵ From a statistical perspective, Hirayama is believed to be one of the first Japanese epidemiologists to use lognormal models in the estimation of time exposures following point source outbreaks.²⁶ Takeshi Hirayama died in October 1995 aged 72 and was remembered by Hong Kong based anti-tobacco advocate, Professor Judith Mackay, as the 'grandfather of Asian epidemiology'.²⁷ Thirty years on, it is timely to remember the achievements of this pioneering individual.

At the end of the day, perhaps the most important outcome of Hirayama's study was that it opened the floodgates for further research into the effects of passive smoking. Research which ultimately proved beyond doubt that tobacco use causes significant harm for not only the smoker, but also for those around them. Hirayama may have now passed on, but his legacy will not be erased.

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