

## RESEARCH ARTICLE

# Tobacco Smoke Exposure and Breast Cancer Risk in Thai Urban Females

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### Abstract

The incidence of urban female breast cancer has been continuously increasing over the past decade with unknown etiology. One hypothesis for this increase is carcinogen exposure from tobacco. Therefore, the objective of this study was to investigate the risk of urban female breast cancer from tobacco smoke exposure. The matched case control study was conducted among Thai females, aged 17-76 years and living in Bangkok or its surrounding areas. A total of 444 pairs of cases and controls were recruited from the Thai National Cancer Institute. Cases were newly diagnosed and histologically confirmed as breast cancer while controls were selected from healthy women who visited a patient, matched by age  $\pm 5$  years. After obtaining informed consent, tobacco smoke exposure data and information on other potential risk factors were collected by interview. The analysis was performed by conditional logistic regression, and presented with odds ratio (ORs) and 95% confidence intervals (CI). From all subjects, 3.8% of cases and 3.4% of controls were active smokers while 11.0% of cases and 6.1% of controls were passive smokers. The highest to lowest sources of passive tobacco smoke were from spouses (40.8%), the workplace (36.8%) and public areas (26.3%), respectively. After adjusting for other potential risk factors or confounders, females with frequent low-dose passive smoke exposure ( $\leq 7$  hours per week) from a spouse or workplace had adjusted odds ratio 3.77 (95% CI=1.11-12.82) and 4.02 (95% CI=1.04-15.50) higher risk of breast cancer compared with non-smokers, respectively. However, this study did not find any association of breast cancer risk in high dose passive tobacco smoke exposure, or a dose response relationship in cumulative passive tobacco smoke exposure per week, or in the active smoker group. In conclusion, passive smoke exposure may be one important risk factor of urban female breast cancer, particularly, from a spouse or workplace. This risk factor highlights the importance of avoiding tobacco smoke exposure as a key measure for breast cancer prevention and control.

**Keywords:** Breast cancer - active smoking - passive smoking - urban female - risk factor

*Asian Pac J Cancer Prev*, 15 (17), 7407-7411

### Introduction

Cancer is a common public health problem at the global and national levels. Worldwide, breast cancer was the most commonly diagnosed neoplasm among women (DeSantis et al., 2011). It is approximately one fourth of all cancers in women (Elmore and Armstrong, 2005). In Thailand, the age standardized incidence rate (ASR) of breast cancer each year was approximately 26.4 persons per 100,000 women. This type of cancer has been found to have the highest incidence in the female population, with the numbers exceeding all other cancers as well, particularly, in Thai urban females. It also commonly occurs in middle-aged females (45-55 years old).

According to the national cancer registry, data showed that Bangkok province had the highest incidence rate of female breast cancer, well over the national average (ASR=41.2) (Khuhaprema et al., 2013). In fact, the overall breast cancer incidence rate in Thailand has been continuously increasing over the past decade. Breast

cancer is a multi-factorial health problem. Although there are many well established risk factors such as reproductive (Parsa and Parsa, 2009) and genetic factors (Mahdi et al., 2013), they only present a modest risk of breast cancer and are difficult to change at the population level. Only few studies focus on the etiology of breast cancer from the perspective of preventable or modifiable risk factors, such as diet (Sangrajrang et al., 2013) and occupation (Ekpanyaskul et al., 2010). Another possible factor is carcinogen exposure from tobacco. Tobacco smoke contains more than 40 chemicals hazards known to be or suspected of being breast carcinogenic substances that can be found in breast milk. Previous studies have shown the biological and toxicological mechanism of carcinogenesis in human and animal mammalian tissue (Reynolds, 2013).

Smoke exposure is one of the largest public health threats in the world. More than five million deaths are the result of direct tobacco use while more than 600,000 are the result of non-smokers being exposed to passive smoke (WHO, 2009). Up to half of those currently exposed to

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direct or indirect tobacco smoke will eventually die of a tobacco-related disease. Smoking is perhaps the single greatest cause of preventable death and can lead to many other diseases, including cancers. In recent decades, many studies have established the relationship between tobacco use and breast cancer. In a recent expert review and soon to be published as IARC Monograph 100E, the list of cancers with 'sufficient' evidence of tobacco smoke as being causative was updated to include the cancers of many organs except breast cancer (Secretan et al., 2009). The toxicological and epidemiological evidence concerning breast cancer and tobacco smoke is controversial, with some studies showing an increase in risk (Terry and Rohan, 2002; Al-Delaimy et al., 2004; Gram et al., 2005; Cui et al., 2006; Ambrosone et al., 2008; Ahern et al., 2009; Luo et al., 2011; Xue et al., 2011) and others not or null associations (Baron et al., 1990; Chen et al., 2005; Yang et al., 2013). Of course, ethical issues prevent determining causation through experimental studies so observational studies were performed in order to prove causation, which is an important step in initiating legal restrictions against smoking. On the other hand, currently, a significant gap exists in the knowledge on tobacco smoke and breast cancer in Thai urban females, who have a different ethnicity from western women and a low prevalence of smoking while still seeing a rising incidence of breast cancer. Therefore, the objective of this study was to investigate the risk of Thai urban female breast cancer from tobacco smoke exposure.

## Materials and Methods

This study was undertaken as a project in breast cancer risk in Thailand and was approved by the ethics committee of the Thai National Cancer Institute. The matched hospital-based case-control study was conducted among Thai females aged over 15 years old and living in Bangkok or its surrounding area. The 444 pairs of cases and controls were recruited from the Thai National Cancer Institute in 2007-2011. Cases were newly diagnosed and histologically confirmed as breast cancer while controls were selected from healthy women who visited the non-breast cancer patients, matched by age  $\pm 5$  years. Informed consent was obtained from all participants. Face-to-face interviews were done by trained interviewers. Standard structured questionnaires were used for both case and controls, with the specific objective of the study being unknown.

Women who had ever regularly smoked at least 50 equivalent cigarettes over a 6 month period of cigarette, pipe, cigar or other local tobacco products, such as Bijak usage, were defined as active smokers. The smokers were asked the age they had started and stopped smoking, if they had stopped before the interview. Non-smokers who were cumulatively exposed to tobacco smoke at least 1 hour per week from any product and from any source such as a spouse, workplace or public area were defined as passive smokers. The quantity per day was calculated by summing the smoke exposure of the total week and dividing by 7 days. The median time of duration of smoking in active smokers and cumulative smoke exposure per week in

passive smokers were utilized as the cut point between low and high exposure.

The other co-variate risk factors were also ascertained to control confounding factors. They consisted of five main areas: personal factors (age, religion, education, marital status, occupation), health status factors (body mass index; BMI, history of breast tissue biopsy), reproductive factors (menstrual status, regularity of menstrual cycle, age at menarche, number of full term pregnancies, age at first delivery, history of abortion in terms of number and age at first abortion, history of breast feeding, use of oral contraceptive pills; OCP), genetic factors (first degree relatives with breast cancer), and lifestyle related factors (exercise, alcohol and grilled food consumption).

The statistical analysis in this study was performed with SPSS, version 21.0 (IBM/SPSS Inc.). For descriptive statistics, each category in each factor of case and control was presented by number and percentage. The chi-square was utilized to test the difference between case and control in each factor. The significant factors with p value less than 0.2 and no multicollinearity were selected to adjust for the confounders in the multivariate analysis accompanied with tobacco exposure history. Conditional logistic regression was utilized by the Cox regression method, and presented with crude and adjusted odds ratio (ORs), and 95% confidence intervals(CI) (Chan, 2005).

## Results

The age of all subjects in this study ranged from 17-76 years. The mean and standard deviation of age in the case group was  $45.84 \pm 10.14$  years while in the control group, it was  $45.70 \pm 10.13$  years. Of all subjects, 61.93% were premenopausal and the rest were menopausal due to natural or surgical causes. The descriptive data of case and control, and the statistical comparison between the two groups, are shown in Table 1.

From the total subjects, 3.8% of cases and 3.4% of controls actively smoked between 1 and 51 years. For passive exposure in 76 persons, 11.0% of cases (49 persons) and 6.1% of controls (27 persons) were passive smokers. The mean  $\pm$  standard deviation and median of passive exposure time was  $11.84 \pm 11.44$  and 7 hours per week, respectively (range 1-56 hours per week). The highest to lowest proportion of passive tobacco smoke sources were from spouses (40.8%), the workplace (36.8%) and public areas (26.3%), respectively.

The following factors from Table 1 were selected as confounders: health status factors such as BMI, history of breast tissue biopsy; reproductive factors such as number of abortions, history of breast feeding, history of OCP usage; genetic factors such as first degree relatives with breast cancer; and lifestyle related factors such as regular exercise, regular consumption of grilled food. After adjusting for these confounders, females who were frequently exposed to passive tobacco smoke had 2.27 times (95%CI=1.30-3.98) higher risk of breast cancer compared with non-smokers while active exposure to tobacco smoke had no statistically significant risk with adjusted odds ratio 1.35 (95%CI=0.57-3.22). When stratified by menstruation status, only premenopause

**Table 1. The Descriptive Data of Case and Control, and the Statistical Comparison between Two Groups**

| Factors                               | Case<br>n=444 (%) | Control<br>n=444 (%) | p-value | Factors   | Case<br>n=444 (%) | Control<br>n=444 (%) | p-value |
|---------------------------------------|-------------------|----------------------|---------|---|-------------------|----------------------|---------|
| Age group (years old)                 |                   |                      |         | Number of full term pregnancy (times)                   |                   |                      |         |
| ≤40                                   | 142 (32.0)        | 145 (32.7)           | 0.96    | Never   | 148 (33.3)        | 144 (32.4)           | 0.82    |
| 41-55                                 | 224 (50.5)        | 220 (49.5)           |         | 1-2   | 215 (48.5)        | 224 (50.5)           |         |
| ≥56                                   | 78 (17.5)         | 79 (17.8)            |         | >2  | 81 (18.2)         | 76 (17.1)            |         |
| Religion                              |                   |                      |         | Age at first time delivery (years old)                  |                   |                      |         |
| Buddhist                              | 426 (95.9)        | 428 (96.4)           | 0.73    | Never   | 148 (33.3)        | 144 (32.4)           | 0.70    |
| Others                                | 18 (4.1)          | 16 (3.6)             |         | 15-30   | 254 (57.2)        | 264 (59.5)           |         |
| Highest level of education            |                   |                      |         | >30   | 42 (9.5)          | 36 (8.1)             |         |
| Nil-6 years schooling                 | 172 (38.7)        | 155 (34.9)           | 0.67    | Number of abortion (times)                              |                   |                      |         |
| 9 years schooling                     | 65 (14.6)         | 68 (15.3)            |         | Never   | 383 (86.3)        | 400 (90.1)           | 0.07    |
| High school                           | 64 (14.4)         | 70 (15.8)            |         | 1-2   | 43 (9.7)          | 32 (7.2)             |         |
| College/Graduation                    | 143 (32.3)        | 151 (34.0)           |         | >2  | 18 (4.1)          | 12 (2.7)             |         |
| Marital status                        |                   |                      |         | Age at first time abortion (years old)                  |                   |                      |         |
| Single                                | 99 (22.3)         | 101 (22.7)           | 0.46    | Never   | 383 (86.3)        | 400 (90.1)           | 0.09    |
| Married                               | 295 (66.4)        | 304 (68.5)           |         | ≤30   | 41 (9.2)          | 35 (7.9)             |         |
| Others                                | 50 (11.3)         | 39 (8.8)             |         | >30   | 20 (4.5)          | 9 (2.0)              |         |
| Major occupation in working life      |                   |                      |         | History of breastfeeding                                |                   |                      |         |
| Housewife/not employed                | 254 (57.2)        | 252 (56.8)           | 0.90    | No children   | 139 (31.3)        | 138 (31.0)           | 0.02    |
| Agriculture/industrial/service sector | 190 (42.8)        | 192 (43.2)           |         | No  | 63 (14.2)         | 38 (8.5)             |         |
| Body mass index                       |                   |                      |         | Yes   | 242 (54.5)        | 269 (60.5)           |         |
| Normal                                | 171 (38.5)        | 172 (38.7)           | 0.07    | History of oral contraceptive pill usage                |                   |                      |         |
| Underweight                           | 32 (7.2)          | 25 (5.6)             |         | No  | 240 (54.1)        | 272 (61.3)           | 0.03    |
| Overweight                            | 84 (18.9)         | 113 (25.5)           |         | Yes   | 204 (45.9)        | 172 (38.7)           |         |
| Obese                                 | 157 (35.4)        | 134 (30.2)           |         | First degree relatives had a diagnosis of breast cancer |                   |                      |         |
| History of breast biopsy              |                   |                      |         | No  | 421 (94.8)        | 437 (98.4)           | 0.005   |
| Never                                 | 402 (90.5)        | 429 (96.6)           | <0.001  | Yes   | 23 (5.2)          | 7 (1.6)              |         |
| Ever                                  | 42 (9.5)          | 15 (3.4)             |         | Regularly exercise                                      |                   |                      |         |
| Menstrual status                      |                   |                      |         | No  | 301 (67.8)        | 240 (54.1)           | <0.001  |
| Premenopause                          | 275 (61.9)        | 275 (61.9)           | 0.89    | Yes   | 143 (32.2)        | 204 (45.9)           |         |
| Natural menopause                     | 143 (32.2)        | 146 (32.9)           |         | Regularly drink alcohol                                 |                   |                      |         |
| Surgical menopause                    | 26 (5.9)          | 23 (5.2)             |         | No  | 418 (94.1)        | 413 (93.0)           | 0.49    |
| Regularity of menstruation            |                   |                      |         | Yes   | 26 (5.9)          | 31 (7.0)             |         |
| Regular                               | 385 (86.7)        | 386 (86.9)           | 0.92    | Regularly eat grilled food                              |                   |                      |         |
| Irregular                             | 59 (13.3)         | 58 (13.1)            |         | No  | 387 (87.2)        | 432 (97.3)           | <0.001  |
| Age of menarche (years old)           |                   |                      |         | Yes   | 57 (12.8)         | 12 (2.7)             |         |
| ≤11                                   | 15 (3.4)          | 16 (3.6)             | 0.39    | Tobacco smoke exposure                                  |                   |                      |         |
| 12-16                                 | 372 (83.8)        | 384 (86.5)           |         | No  | 378 (85.2)        | 402 (90.5)           | 0.03    |
| >16                                   | 57 (12.8)         | 44 (9.9)             |         | Active  | 17 (3.8)          | 15 (3.4)             |         |
|                                       |                   |                      |         | Passive   | 49 (11.0)         | 27 (6.1)             |         |

**Table 2. Crude and Adjusted Odds Ratio with 95% Confidence Interval of the Association between Smoking Status and Breast Cancer Risk, Stratified by Menopausal Status**

| Smoking status | Total subjects (n=888) |                          | Pre-menopause group (n=550) |                          | Post-menopause group (n=338) |                          |
|----------------|------------------------|--------------------------|-----------------------------|--------------------------|------------------------------|--------------------------|
|                | Crude ORs<br>(95%CI)   | Adjusted ORs*<br>(95%CI) | Crude ORs<br>(95%CI)        | Adjusted ORs*<br>(95%CI) | Crude ORs<br>(95%CI)         | Adjusted ORs*<br>(95%CI) |
| Non-smoker     | reference              | reference                | reference                   | reference                | reference                    | reference                |
| Active smoker  | 1.33(0.63-2.85)        | 1.35(0.57-3.22)          | 1.07(0.40-2.84)             | 1.11(0.37-3.34)          | 2.50(0.49-12.87)             | 3.10(0.40-23.93)         |
| Passive smoker | 1.97(1.19-3.24)        | 2.27(1.30-3.98)          | 1.88(1.02-3.50)             | 2.13(1.04-4.33)          | 1.80(0.60-5.37)              | 2.99(0.89-10.14)         |

\*Adjusted for BMI, history of biopsy, number of breast biopsy, history of breastfeeding, history of OCP usage, family history of breast cancer, regularly exercise, and regularly eat grilled food

**Table 3. Crude and Adjusted Odds Ratio with 95% Confidence Interval of the Association between Source of Passive Smoke and Breast Cancer Risk**

| Source                             | Model 1: Active smoker & Passive smoker exposure from spouse* |                          | Model 2: Active smoker & Passive smoker exposure from workplace* |                          | Model 3: Active smoker & Passive smoker exposure from public areas* |                          |
|------------------------------------|---|--------------------------|--|--------------------------|---|--------------------------|
|                                    | Crude ORs<br>95% CI   | Adjusted ORs<br>95% CI** | Crude ORs<br>95% CI  | Adjusted ORs<br>95% CI** | Crude ORs<br>95% CI   | Adjusted ORs<br>95% CI** |
| No exposure                        | reference   | reference                | reference  | reference                | reference   | reference                |
| Active smoke exposure (years)      |   |                          |  |                          |   |                          |
| ≤12                                | 1.73 (0.61-4.88)  | 1.32 (0.41-4.29)         | 1.67 (0.58-4.85)   | 1.2 (0.36-4.00)          | 1.57 (0.55-4.49)  | 1.14 (0.34-3.78)         |
| ≥12                                | 1.19 (0.40-3.49)  | 1.31 (0.38-4.52)         | 1.09 (0.35-3.44)   | 1.11 (0.31-4.04)         | 1.08 (0.34-3.40)  | 1.12 (0.30-4.24)         |
| Passive smoke exposure (hour/week) |   |                          |  |                          |   |                          |
| ≤7                                 | 3.54 (1.16-10.76)   | 3.77 (1.11-12.82)        | 4.39 (1.24-15.52)  | 4.02 (1.04-15.50)        | 1.72 (0.62-4.74)  | 2.21 (0.72-6.79)         |
| ≥7                                 | 1.13 (0.32-4.04)  | 0.89 (0.22-3.64)         | 0.63 (0.18-2.20)   | 1.23 (0.32-4.78)         | 1.00 (0.14-7.10)  | 1.35 (0.15-12.53)        |

\*The passive smokers from other sources were excluded; \*\*Adjusted for BMI, history of breast biopsy, number of abortion, history of breastfeeding, history history of OCP usage, family history of breast cancer, regularly exercise, and regularly eat grilled food

females frequently exposed to passive tobacco smoke were also at higher risk of breast cancer compared with non-smokers (Table 2).

The risk of active and passive smoke exposure from various sources was not a statistically significant risk. However, when stratified by degree of exposure, the low dose of passive smoke exposure from a spouse or workplace had adjusted odds ratio 3.77 (95%CI=1.11-12.82), 4.02 (95%CI=1.04-15.50) higher risk of breast cancer compared with non-smokers, respectively. This

study did not find an association of breast cancer risk in high dose passive tobacco smoke exposure, the dose response relationship in cumulative passive tobacco smoke exposure per week, or in the active smoker group (Table 3).

## Discussion

Smoking is one of the preventable and modifiable risk factors in many diseases, including breast cancer,

which is the leading cancer in Thai urban women, and can lead to mortality even in non smoking women. This study was to elucidate the association between smoke exposure and urban female breast cancer risk. The result from the subjects in this study shows the smoking rate, both active and passive smoking, is not much different from the national survey (Sangthong et al., 2011; CDC, 2012). The prevalence rate was still lower than in western countries (CDC, 2012). The prevalence of passive smoker was higher than active smoker due to the higher active smoking rate in men than women. Smoking as a risk factor of breast cancer is still ambiguous. The epidemiological studies show that passive smoke is associated with breast cancer risk. The result of this relationship is consistent with studies done in the West such as by the California Air Resources Board (Johnson et al., 2011) and the United States Surgeon General (U.S. Department of Health and Human Services, 2006) as well as studies in Asia such as a recent study in China (Chen, 2014). Smoke exposure could be related to reproductive factors. In the present study, only early exposure in the reproductive period could be a breast cancer risk. The risk of passive smoke in premenopausal women in this study was also consistent with other studies (Hanaoka et al., 2005; Johnson et al., 2011). Human breast tissue is sensitive to environmental carcinogens in the premenopausal period, during periods of rapid cell proliferation during puberty when that differentiation is incomplete, and when complete cellular differentiation is never achieved in nulliparity women (Reynolds, 2013).

Smoke from a spouse or the workplace in this study indicates that these two factors are important sources of breast cancer risk in Thai women. The result is consistent with Western women but different in level of exposure (Luo et al., 2011; Reynolds et al., 2009). The immediate implication is that there should be a strong focus on preventing smoke exposure. An ecological study indicated that higher percentages of women working and living in smoke-free environments had lower breast cancer rates (Piazza and Hyland, 2011). In Thailand, there is increasing legislation to guarantee smoke-free areas such as in restaurants, but it is difficult to apply these laws in practice, and in the home, it is almost impossible to legislate yet alone enforce anti-smoking regulations. Critically, however, it is these two very sources of passive smoke exposure, from a spouse or the workplace, that are responsible for most passive exposure. Urgently, effective measures are needed to control both smoking and smoke exposure in the home and the workplace.

On the other hand, this study did not find an association between active smoking and breast cancer risk. The result is consistent with a meta-analysis study of Chinese women (Chen, 2014). It may be difficult to describe the causal relationship between passive smoking and breast cancer risk. One possible explanation for the non-association in active smokers is that tobacco smoke might have different effects on breast cancer risk in smokers compared to those who are exposed to passive smoke. Mostly, people sense that passive smoke, which is more diluted than actively inhaled smoke, is responsible for a small fraction of the added risk of health effects among active smokers; however, the scientific data show that passive smoke

presents a stronger breast cancer risk than lung cancer (Johnson, 2008). The smoke has two forms that come from burning tobacco: sidestream smoke, which burns from the end of a cigarette, pipe, cigar or other local tobacco products such as Bijak; and mainstream smoke, which is exhaled by a smoker. Differences in conditions during smoke formation were found to contribute to a remarkable discrepancy of physicochemical compositions between both forms (Collishaw et al., 2009). Sidestream smoke has higher concentrations of carcinogens than mainstream smoke. The vapor-phase constituents are more quickly absorbed into the blood and lymph systems than particulate-phase constituents that are predominantly found in mainstream smoke, making a predominate and more plausible effect of passive smoke on breast carcinogenesis than actively smoking (Schick and Glantz, 2005). Moreover, the active smokers did not have a higher breast cancer risk in this study, most likely, because the small sample size of smokers, due to the low prevalence of Thai female smokers, skewed the analysis for statistical significance in this study.

The limitation is selection bias. This study was conducted in The National Cancer Institute of Bangkok, where all of the patients are cancer patients. Thus, control selection could not be selected as in a hospital-based case control study, a visiting control was used. The control group may differ from the case group in education level, which might raise their awareness of health issues, including smoke exposure. Nevertheless, there is no difference between educational level in both groups, and tobacco exposure is also not different in education level. In the tobacco exposure assessment, the self report could lead to recall bias and cause misclassification. To avoid this recall bias, this study used the recent year of exposure and intensity information from the criteria to classify. Recall bias could still be present; especially, geriatric subjects can not recall the past events. This might cause a lack of association to be found in the post menopausal group. However, the information bias could occur less frequently. Tobacco smoke exposure data and other potential risk factors were collected by interviews, without subjects knowing the specific objective of the study, and the prevalence of active and passive smokers was not abnormal in proportion to national statistics as well. Cohort studies could be conducted, which have the advantage of avoiding the possibilities of selection bias, recall bias, and exposure assessment. Further research such as with large numbers of cases, suspected increased susceptibility, and quantitative exposure assessment would help to better clarify and quantify the tobacco risks for breast cancer.

Passive smoke and breast cancer risk is an emerging public health issue and it impacts urban women. It requires a greater awareness of the dangers of passive smoke through public health campaigns. Scientific evidence has proven that there is no safe level of exposure to passive smoke (WHO, 2009). Short period exposure could also be harmful. Therefore, to prevent smoke exposure causing breast cancer, the primary prevention activity should be, absolutely, to eliminate smoke in the environment by decreasing the number of smokers and enforcing

legislation requiring 100% smoke-free in enclosed areas. In addition, preventive methods to promote the avoidance of environmental smoke exposure such as conducting educational initiatives to reduce passive exposure in homes and public awareness campaigns about the dangers of passive smoke can be as important as prohibitive ones against passive smoke and smoking. The secondary prevention activity should be to educate those exposed and to perform regular breast cancer screenings. In conclusion, this study suggests that passive smoke exposure is one important risk factor of Thai urban female breast cancer, particularly, exposure from a spouse or workplace. This risk factor shows the importance of avoiding tobacco smoke exposure as a key of breast cancer prevention and control.

### Acknowledgements

This work was supported by the Faculty of Medicine, Srinakharinwirot University and the Thai National Cancer Institute. The authors declare no conflict of interest and would like to thank to Mr. Ronald Stefan for proofreading the article.

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