Passive or active smoking, which is more relevant to breast cancer

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ABSTRACT

Objectives: To examine the risk of breast cancer associated with passive and active smoking and to explore risk heterogeneity among studies.

Methods: We conducted this study in Iran during the year 2006. Fifteen published studies on smoking and breast cancer met the defined criteria. Pooled odds ratio (OR) estimates for female breast cancer were calculated. The active and passive smokers were compared with women categorized as never regularly exposed to tobacco smoke.

Results: The pooled risk estimate for breast cancer associated with passive smoking among non-smokers was 1.38 (95% confidence interval [CI]; 1.16-1.65). The pooled OR for active smokers was 1.25 (95% CI; 1.11-1.41). Also, the combined OR for passive and active smokers related to breast cancer was 1.30 (95% CI; 1.17-1.45).

Conclusion: Based on the results of the pooled analysis, it can be concluded both passive and active smoking equally increase the risk of female breast cancer.

Saudi Med J 2007; Vol. 28 (2): 254-258

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Received 18th June 2006. Accepted 24th October 2006.

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Environmental factors may play an important role in the etiology of female breast cancer. The risk of breast cancer with smoking is strong in families with a history of breast cancer, ovarian cancer, or both.[1] Cigarette smoking has been examined as a possible risk factor for breast cancer for over a decade.[2] Indeed, subsequent studies consistently showed that women exposed to passive smoking (exposure to second-hand smoke) are at increased risk of breast cancer compared with women never exposed to either active or passive smoke.[2-7] The association of breast cancer both with active smoking and with passive was even of a similar order of the magnitude of approximately 2-fold.[2] In contrast, in a large case-control study, there was no relationship between cigarette smoking and breast cancer.[8] A review of published studies suggests that both active and passive smoking may increase the risk of breast cancer, particularly pre-menopausal breast cancer.[9,10] Most studies of smoking and breast cancer report null or weak positive associations limited to specific subgroups of women,[3-6,8,11-17] whereas others report weak inverse associations.[8,17,18] Although both active and passive smoking are known to increase the risk of lung cancer, findings for breast cancer have been mixed and the role of active and passive smoking in breast cancer remains controversial. However, the effects are not fully understood and more research is needed.[19] To summarize the epidemiological evidence for a causal association between smoking and breast cancer and consider recent studies on the effects of active and passive exposure to cigarette smoke on breast cancer, a meta-analysis study was conducted. According to controversies, in the present study, first the risk of active and passive smoking will be examined and then compared according to selected case-control studies.

Methods. We conducted this study in Iran during the year 2006. We Included in the meta-analysis only retrospective studies that contained data on breast cancer related to smoking. A systematic review of the literature was started by identifying a broad set of studies through Medline and EMBASE for the period January 1988, until May 2006, and by manual searches of relevant journals and of reference lists of retrieved articles. The electronic search used the terms 'Breast cancer', 'passive smoking' and 'active smoking' to find additional data in more reports. A broad search yielded

more than 500 potentially relevant titles. A manual review of titles and abstracts identified more than 45 articles that we thought could contain data on relevant outcomes. By reviewing these articles, we identified a total of 15 peer-reviewed studies that contained data on breast cancer and smoking. The inclusion and exclusion criteria for selecting of the studies were as follows: The searches were limited to studies published in English. Titles, abstracts, and subject headings in the database were investigated using the keywords breast cancer and smoking. The total numbers of case and control and odds ratio (OR) have been reported. At least one of the terms of "environmental tobacco smoking", "current smoker", "never smoker", "ever smoker" or "tobacco smoking" were applied. We did not attempt to locate unpublished studies. The disease was breast cancer and did not refer to any stage or classification of cancer. In all the case-control studies, if the study sample was found to overlap or come from the same study project, only the paper with the largest sample size was retained. If both hospital and population controls were used for comparison separately, the result of the population control was chosen for the analysis. Two researchers performed data collection and extraction independently. Differences in data extraction were resolved by discussion.

In order to summarize what is known regarding the link between smoking and breast cancer, we pooled information from 15 published studies.[4,6,8,14,20-31] The studies were published by the period; they included only case-control studies. Meta-analysis is a statistical analysis that combines or integrates the results of several studies to provide pooled information regarding the subject.[32] Analysis involved the calculation of a common estimate of OR between breast cancer and smoking with 95% confidence interval (CI). Directional zero-effect test using Chi-square was used to test the null hypothesis that all effects are zero versus the alternative that all studies had the same, non-zero effect. Also, effect-equality test using Cochran's Q was applied for testing the null hypothesis that all effects are equal (homogeneous) versus the alternative that at least one effect had a different effect (heterogeneous). This test is used to choose between the use of a fixed effect (homogeneous) model and a random effect (heterogeneous) model. Analysis was performed with a fixed effects model, but consistency was checked with a random effects model. The meta-analysis was performed using NCSS and PASS 2000 Released December 2005.

Results. This meta-analysis consists of 34947 women with breast cancer as the case group and 57654 women as the control group. **Table 1**, shows the selected studies, including type of exposure, OR and confounding variables considered in the studies. **Table 2** shows the OR and zero-effect test for passive exposures and active

Table 1 - Characteristics of case-control studies of smoking on breast cancer from published studies.

Study	Kind of exposure	Case	Control	Odds ratio (95% CI)	Confounding variables considered
Kropp S, 2002[24]	Passive	153	310	1.61 (1.08-2.39)	Alcohol intake, Breastfeeding, Education, Menopausal status, Body mass index (BMI)
Kropp S, 2002[24]	Active	271	643	1.25 (0.76-1.74)	Alcohol intake, Breastfeeding, Education, Menopausal status, Family history, BMI
Lash T, 1999[6]	Passive	80	267	2.0 (1.1-3.7)	Age, Alcohol intake, BMI, Family history, Parity
Lash T, 1999[6]	Active	54	147	2.4 (1.1-5.5)	Age, Alcohol intake, BMI, Family history, Parity
Morabia A, 2000[30]	Passive	38	36	1.9 (0.7-4.6)	Age, Education, BMI, Oral contraception, Family history, Menarche age
Morabia A, 2000[30]	Active	46	34	2.7 (1.1-6.6)	Age, Education, BMI, Oral contraception, Family history, Menarche age
Liu L, 2000[25]	Passive	186	186	1.54 (1.0-2.37)	Age, BMI
Friedenreich C, 2001[23]	Passive	382	399	1.41 (0.99-2.02)	Alcohol intake, Age
Marcus P, 2000[26]	Passive	864	790	1.1 (0.9-1.3)	Age, Alcohol intake
Field N, 1992[22]	Active	1617	1617	1.03 (0.9-1.19)	Age, Menopausal status
Band P, 2002[20]	Active	318	340	1.69 (1.13-2.51)	Age, Menopausal age
Schechter M, 1989[28]	Active	126	379	1.2 (0.8-2.0)	Age, Menopausal status
Braga C, 1996[21]	Active	2569	2588	1.14 (0.9-1.4)	Age, Menopausal status
Baron J, 1996[8]	Active	5307	7268	1.1 (1.01-1.19)	Age, Menopausal status
Meara J, 1989[14]	Active	118	118	2.9 (1.16-7.25)	Age, Alcohol consumption
Innes K, 2001[29]	Active	319	768	2.7 (1.1-6.3)	Age, Race, Education
Morabia A, 1996[4]	Active	244	1032	4.6 (2.2-9.7)	Alcohol, Saturated fat intake, Age
Hamajima N, 2002[31]	Active	22255	40832	1.03 (0.98-1.07)	-

Table 2 - Odds ratio (OR) and confidence interval (CI) for exposure type and breast cancer risk from published studies.

Type of exposure	OR and 95% CI			Zero effect test		
	OR	Lower	Upper	Chi-Square	df	*P*-value
Active	1.25	1.11	1.41	13.84	1	$p<0.001$
Passive	1.38	1.16	1.65	14.46	1	$p<0.001$
Combined	1.30	1.17	1.45	18.86	1	$p<0.001$

df - degrees of freedom

Table 3 - Effect-equality (heterogeneity) test for passive and active smoking related to breast cancer.

Kind of exposure	Outcome measure	Cochran's Q	df	*P*-value
Active	Odds Ratio	47.71	11	<0.001
Passive	Odds Ratio	5.83	5	0.32
Combined	Odds Ratio	62.98	17	<0.001

df - degrees of freedom

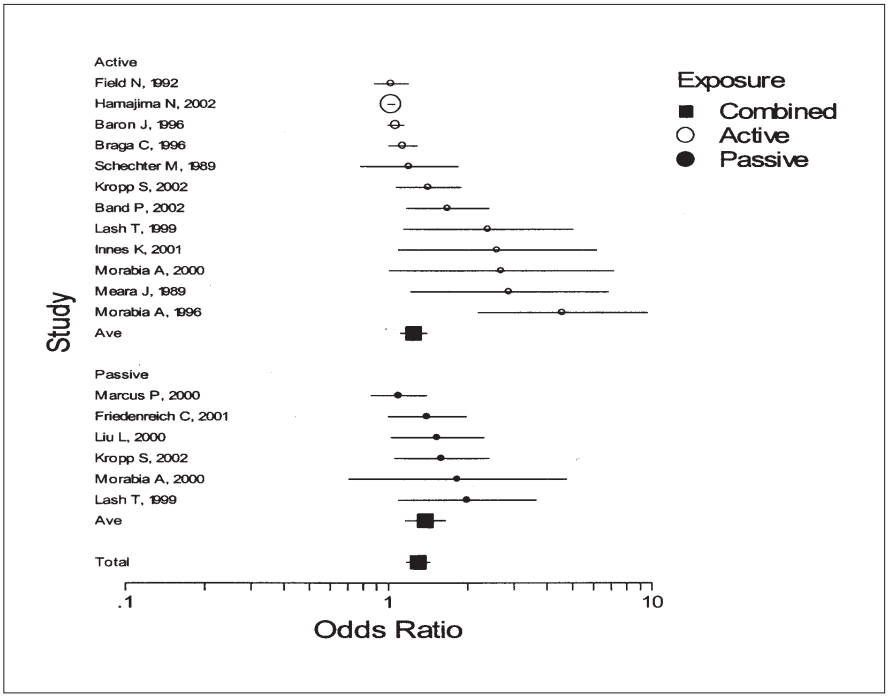

Figure 1 - Forest plot of odds ratio for passive and active smoking articles related to breast cancer.

exposures as well as combined related to breast cancer. Although, the OR for the passive smokers is higher than the active smokers, there is no significant difference between the 2 groups (p=0.75). The chi-square values show that all studies had the same, non-zero effect (p-value<0.001). **Table 3** shows heterogeneity tests for passive and active smoking related to breast cancer, and illustrates that all effects are equal for passive smokers whereas at least one effect had a different effect (heterogeneous) for active smokers. This table shows that there are controversies in different studies. **Figure 1** shows the forest plot of OR for the studied reports. Also, it shows OR for passive and active smoking articles related to breast cancer, separately.

Discussion. In this meta-analysis, we found an association between passive and also active smoking with breast cancer. The strength of our study is meta-analysis design, its size, and its comparison between passive and active exposures. Our meta-analysis were based on 15 case control studies. Cigarette smoking has been suggested as a cause of breast cancer, but many studies addressing the relationship have yielded inconsistent results. A possible explanation is that many of these studies have overlooked the potential effects of passive exposure to cigarette smoke when assessing the effects of active smoking.[33,34] Also, the effect of tobacco smoking on the occurrence of breast cancer has been the topic of some debate. Until the 1990s, most case-control and cohort studies examining the association between cigarette smoke exposure and breast cancer focused on active smoking. These studies did not adequately ascertain the whole-of-life Environmental

Tobacco Smoke (ETS) exposure of the participants.[33,35] Also, in an even larger population-based, case-control study in Switzerland, Morabia et al[4] found an elevated risk of breast cancer incidence among non-active women smokers. As well, Lash and Aschengrau,[6] in a case-control study of women diagnosed with breast cancer found that passive smokers were twice as likely to be diagnosed with breast cancer as women who had not been exposed to ETS. Similar results were obtained by Chang-Claude, Johnson and Terry.[2,7,9]

One of the important limitations of other studies was the small number of cases and hence imprecision of the results. This highlights the importance of pooling results from all studies to provide a precise estimate of the overall effect. Other limitations applicable to most of the studies include possible recall bias in case-control studies, failure to use a consistently unexposed group for the referent, uncertainty in exposure quantification, possible uncontrolled confounding, and failure to adjust for genetic susceptibility. Many of these limitations also apply to this study. Also, there are several reasons why passive smoking could cause breast cancer in women, even though some studies of active smoking have not revealed a positive association with breast cancer. First, previous studies of active smoking have included nonsmokers exposed to ETS in the referent group, potentially obscuring an association between active smoking and breast cancer. A second possible explanation for the different effects of ETS and mainstream smoke on breast cancer risk is that the age at first exposure may modify the effect of exposure on breast cancer risk. Women may be at greatest risk from both ETS and mainstream smoke early in life, when the breast tissue is growing most rapidly.[4,5] Also, tobacco-specific nitrosamines and certain other carcinogens are more concentrated in ETS than in mainstream smoke.[36] Therefore, it is possible that exposure to ETS confers greater risk than active smoking alone. It is important to note that measures of smoking may vary considerably between the studies. For example, total lifetime exposure, years smoked by spouse, exposure at home and work, smoking prior to first pregnancy and age at first exposure, are the factors that may affect breast cancer.

Based on the results of pooled analysis, it can be concluded both passive and active smoking equally increases the risk of female breast cancer. Clearly, further studies are needed to investigate the effects of active and passive exposure to cigarette smoke based on total lifetime exposure, years smoked by spouse, exposure at home and work, smoking prior to first pregnancy and age at first exposure.

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