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Active and Passive Smoking and Risk of Breast Cancer by Age 50 Years among German Women

Silke Kropp and Jenny Chang-Claude

From the Department of Clinical Epidemiology, German Cancer Research Center, Heidelberg, Germany.

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Recent studies suggest that both active and passive smokers have an increased risk of breast cancer compared with women who have never been either actively or passively exposed. Data on lifetime active and passive smoking were collected in 1999–2000 from 468 predominantly premenopausal breast cancer patients diagnosed by age 50 years and 1,093 controls who had previously participated in a German case-control study conducted in 1992–1995. Compared with never active/passive smokers, former smokers and current smokers had odds ratios of 1.2 (95% confidence interval (CI): 0.8, 1.7) and 1.5 (95% CI: 1.0, 2.2), respectively, and ever active smokers had an odds ratio of 1.3 (95% CI: 0.9, 1.9). The risk increased with duration of smoking and decreased after cessation of smoking. Among never active smokers, ever passive smoking was associated with an odds ratio of 1.6 (95% CI: 1.1, 2.4). Exposure to environmental tobacco smoke during childhood or before the first pregnancy did not appear to increase breast cancer risk. At greatest risk were women who had a high level of exposure to both passive and active smoking (odds ratio = 1.8, 95% CI: 1.2, 2.7). This study strengthens the hypothesis of a causal relation between active and passive smoke exposures and breast cancer risk.

breast neoplasms; case-control studies; premenopause; smoking; tobacco smoke pollution; women

Abbreviations: CI, confidence interval; OR, odds ratio.

Ever since overwhelming evidence linked tobacco smoking with lung cancer, special attention has been paid to smoking as a putative risk factor for various cancer sites. Many studies have since linked smoking with cancer in organs not in direct contact with inhaled smoke (1, 2).

Numerous studies implicated the possibility of a role of tobacco constituents in breast carcinogenesis. Nicotine and cotinine were found in breast milk (3) and breast fluid of smokers (4, 5) and were observed to exhibit mutagenic activity (6). On the other hand, lower urinary estrogen levels were detected among smokers compared with nonsmokers (7). Smoking was thus hypothesized to have an antiestrogenic effect, thereby lowering breast cancer risk in a manner not fully understood (2, 7–9). However, the relative risk estimates of a large number of studies were contradictory but predominantly around unity (10). A possible explanation could be that the protective effect via lowered estrogen levels may be counterbalanced by other harmful mechanisms (11, 12). The discordance of study results considering only active smoking and breast cancer risk prevails up into the recent past (9, 13, 14).

An effect of environmental tobacco smoke on breast cancer risk was first suggested in the 1980s, after observations of an increased risk for women married to smokers compared with women married to nonsmokers (15, 16). Wells (17) proposed that the inconsistency of past results on the association between smoking and breast cancer risk was attributed to the inclusion of passively exposed women into the reference group, thus masking the effects of active smoking.

Four subsequent case-control studies that considered the effect of passive smoking as well as active smoking on breast cancer risk reported elevated odds ratios around 2.0 for active smoking when comparing active smokers with nonactively, non-passively exposed women (18–21). All four studies found elevated risks of similar magnitudes also for passive smoking among never active smokers, although not all results achieved statistical significance. However, breast cancer mortality was not found to be associated with passive

Correspondence to Dr. Jenny Chang-Claude, Im Neuenheimer Feld 280, Department of Clinical Epidemiology, Deutsches Krebsforschungszentrum, 69120 Heidelberg, Germany (e-mail: j.chang-claude@dkfz.de).

smoking in a prospective study that compared women who were married to smokers with women who were married to nonsmokers (22). Another prospective study analogously reports no effect of passive smoking on the incidence of breast cancer (23). However, these authors based their analyses in part on current exposure status data obtained up to 14 years preceding the diagnosis of breast cancer. In addition, they did not consistently use a reference group of lifetime nonexposed women when analyzing the effects of active or passive smoking, which makes comparisons with the mentioned case-control studies difficult.

Apart from the study of Smith et al. (18), which included only women under the age of 36 years, all other studies included predominantly postmenopausal women. We conducted a case-control study of German women up to the age of 50 years to quantify the association between active and passive tobacco smoke exposure and breast cancer risk among younger women.

MATERIALS AND METHODS

The present study was based on a breast cancer case-control study carried out between January 1, 1992, and December 31, 1995, in two regions in southern Germany, "Rhein-Neckar-Odenwald" and "Freiburg" (24). In this preceding population-based study, complete ascertainment of German-speaking women residing in the two study areas with incident in situ or invasive breast cancer diagnosed under the age of 51 years was achieved by surveying 38 hospitals that serve the population of the two regions. Of the 1,005 living, eligible case subjects identified by frequent monitoring of hospital admissions, surgery schedules, and pathology records, 706 (70.2 percent) took part. Of the patients who did not participate, 51 (5.1 percent) were due to refusal of physicians to allow contact, 11 (1.1 percent) were due to health problems, 152 (15.1 percent) refused to participate, and 85 (8.5 percent) did not respond. The median time between diagnosis and interview was 2 months.

For every patient, two controls matched by age and study region were selected randomly from lists of female residents obtained from the population registries of each study region. They were immediately contacted by letter, and 1,381 (61.2 percent) participated. Of the 2,257 eligible controls, 218 (9.7 percent) did not respond, and 658 (29.1 percent) refused to take part. All study participants gave their informed consent. The study was reviewed by the ethics committee of the University of Heidelberg.

The participants completed a self-administered questionnaire assessing demographic, anthropometric, and other known or putative risk factors. Five questions pertaining to active smoking assessed whether the women had ever smoked at least one cigarette a day for at least 1 year, the onset and end of smoking, the duration of a potential temporary cessation of smoking, and the average daily amount of cigarettes smoked.

To obtain detailed information for the present study on lifetime active as well as passive smoking history, all participants were recontacted by letter in August 1999 and invited to take part in a computer-assisted telephone interview. A follow-up through the population registries had been performed to receive changed addresses. The date of death of the 115 deceased cases and three deceased controls was ascertained.

The interviews were conducted by ZUMA (Center for Public Polls, Methods, and Analyses) in Mannheim, Germany, from September 1999 to May 2000 by trained interviewers blinded to the case-control status of the participant. Of the original study population from the years 1992–1995, 66.3 percent of the cases and 79.2 percent of the controls reparticipated in this aspect of the investigation. Nonparticipating cases were deceased (16.3 percent), had invalid telephone numbers (2.7 percent), refused participation (8.3 percent), or could not be reached (6.4 percent). Nonparticipating controls were deceased (0.2 percent), had invalid telephone numbers (2.5 percent), refused participation (12.3 percent), or could not be reached (5.8 percent).

Unlike the first questionnaire, there was no restriction on the amount of cigarettes consumed for a woman to be regarded as a regular smoker; rather, an attempt was made to record every cigarette smoked. Women were asked when they began smoking, the type of product, the amount and frequency of tobacco usage, the intensity of inhalation, and the date of cessation or change in their smoking habit. In the case of a change, the same questions were asked again for the following phase, allowing up to eight different phases of active smoking habits.

Passive smoking was structured into three sections: exposure in the childhood household, in the adult household, and at work. For exposure during childhood, information was elicited on how many smoking persons had lived in the household, the onset of and age at exposure, the number of hours and days each of the persons had smoked in the presence of the participant (thereby distinguishing between week days and weekend days), and the smokiness of the room. Childhood exposure was truncated at 18 years, and exposure data beyond this age were added to the adult household exposure.

For the adult household, information was sought on whether the women had lived with a smoking partner, the onset and end or change of smoking exposure, the daily amount and type of tobacco product smoked, the number of hours and days of passive exposure, and the smokiness of the room. If there had been a change in the smoking habits of the partner, questions were reasked for up to eight varying phases. Additionally, for exposure due to other household members, the same questions were asked as for childhood exposure. Exposure at work was also assessed as for childhood. Here, also, up to eight different phases of smoke exposure were possible. Adult exposure comprised childhood exposure over the age of 18 years, exposure through a partner or other household members, and at work.

All information was truncated at the reference date, which was the date of diagnosis for cases and the date of completion of the first questionnaire for controls. Menopausal status was assigned according to the reported state half a year before the reference date. The menopausal status of women with previous hysterectomy not accompanied by bilateral oophorectomy was not identifiable and classified as unknown.

TABLE 1. Comparison between original and present study distributions of demographic characteristics and potential risk factors in a population-based case-control study of breast cancer, Germany, 1992–1995

	Present study participants		Original study participants	
	Cases (n = 468)	Controls (n = 1,093)	Cases (n = 706)	Controls (n = 1,381)
Mean age (years) at diagnosis/recruitment	43.0	42.7	42.5	42.6
Mean body mass index (weight (kg)/height (m)^2)	23.9	24.2	24.1	24.2
Mean age (years) at menarche	13.1	13.1	13.1	13.1
Age (years) at first birth*	24.3	24.5	24.2	24.3
	%	%	%	%
Study region				
Rhein-Neckar-Odenwald	70.9	68.5	70.0	69.3
Freiburg	29.1	31.5	30.0	30.7
Menopausal status				
Premenopausal	76.9	81.1	79.0	80.8
Postmenopausal	6.8	6.1	6.1	6.7
Unknown	16.2	12.9	14.9	12.5
Education level				
Low	13.2	12.7	14.7	14.2
Intermediate	65.2	62.9	63.3	60.3
High	21.6	24.4	22.0	25.5
Parity				
0	17.7	18.8	21.7	20.8
1	28.8	25.0	29.0	24.5
2	42.5	39.3	38.5	38.0
≥3	10.9	16.8	10.8	16.7
Use of oral contraceptive				
No	18.2	19.6	18.1	19.8
Yes	79.7	79.1	80.0	79.1

Table continues

Odds ratios and 95 percent confidence intervals were computed using multivariate conditional logistic regression analysis. Estimates were produced by the PHREG procedure of the statistical software package, SAS release 6.12 (SAS Institute, Inc., Cary, North Carolina). Analyses were performed with stratification for age in 1-year intervals to optimize age adjustment.

An ever active smoker was defined as having smoked more than 100 cigarettes in her lifetime. Ever passive smokers were women with an average exposure of passive smoke of more than 1 hour a day for at least 1 year in either childhood or adulthood. To obtain this average exposure, we multiplied the average hours per day of each exposure phase by the duration in years of that phase and then calculated the sum over all phases separately for childhood and adulthood. This sum was divided by the total years of passive smoke exposure and yielded an averaged daily exposure in hours. The missing data on hours per day of 98 women, specifically 7.7 percent of the cases and 5.7 percent of the controls, were replaced with the mean hours per day of exposed controls for the particular source of exposure.

The reference group for all analyses comprised never active, never passive smokers. In analyses concerning active smoking, a separate category of only passively exposed women was always included in the model. Active smokers were excluded in analyses of passive smoking. Participants were dichotomized into high and low active exposure by the mean of smoking controls, which was 7 pack-years (the number of packs per day multiplied by the number of years of smoking exposure). Similarly, for the categories of high and low passive exposure (for the sources childhood, partner, and work), the average daily hours of environmental tobacco smoke multiplied by the years of exposure were above or below the mean of passively exposed controls of 75 hours/day-years (number of hours of environmental tobacco smoke exposure per day multiplied by the number of years of exposure).

The following terms were included in the multivariate analyses: total number of months of breastfeeding and body mass index as continuous variables, education (classified into low, intermediate, and high, according to type of schooling attained and the subsequently obtained profes-

TABLE 1. Continued

	Present study participants		Original study participants	
	Cases (n = 468)	Controls (n = 1,093)	Cases (n = 706)	Controls (n = 1,381)
Total duration (months) of breastfeeding*				
0	30.6	29.2	31.3	29.2
1–12	61.3	57.1	61.5	57.7
≥13	8.1	13.7	7.2	13.1
Family history of breast cancer†				
No	85.9	94.4	87.7	94.9
Yes	14.1	5.6	12.3	5.1
Daily average alcohol intake (g)				
0	22.4	17.8	21.7	17.3
1–18	63.9	73.7	63.8	74.1
≥19	13.7	8.5	14.5	8.7
Daily no. of cigarettes‡				
0	45.9	48.2	46.2	46.7
1–10	24.1	23.8	23.4	24.4
11–20	22.2	20.7	21.4	21.5
≥21	7.7	7.3	9.1	7.4
Tumor grading				
Well differentiated	9.2		7.4	
Well-moderately differentiated	2.1		1.6	
Moderately differentiated	41.7		40.9	
Moderate-poor differentiation	1.9		2.0	
Poorly differentiated	28.6		33.0	
Missing	15.0		15.2	

* Among parous women.
† Mother or sister had breast cancer.
‡ Data from first questionnaire.

sional degree), first degree family history, menopausal status (postmenopausal, premenopausal, and unknown), and average daily alcohol intake (categorized as 0, 1–18, and ≥19 g/day). Other factors such as number of full-term pregnancies, study region, use of oral contraceptives, age at first full-term pregnancy, and age at menarche did not influence the estimates and were therefore not included in the statistical models.

The interaction of smoking variables with covariables was tested using the difference of deviances of the models with and without the multiplicative interaction terms (25). The effect of smoking variables on breast cancer risk was not modified by level of education or by alcohol consumption. Tests for trend were performed by scoring the included categories and entering this ordinal variable in the regression analysis.

RESULTS

The distribution of several relevant variables among the 468 cases and 1,093 controls participating in this study closely ressembles that for the original study population (table 1). In particular, there was no appreciable difference in the daily number of cigarettes reported in the first questionnaire. The mean age of the participants at the telephone interview was 43.0 years for cases and 42.7 years for controls.

The proportion of ever active smokers was the same among cases and controls, that is, 57.9 percent (table 2). There was, however, a difference in proportion of those ever exposed only passively (32.7 percent of cases vs. 28.4 percent of controls) and in those neither actively nor passively exposed (9.4 percent of cases vs. 13.2 percent of controls). Most of the women who actively smoked were also passively exposed through other sources; only 5.8 percent of cases and 7.5 percent of controls reported being only active smokers. Passive exposure during childhood was reported by 48.5 percent of cases and 50.0 percent of controls, and passive exposure during adulthood was reported by 79.1 percent of cases and 71.2 percent of controls.

Compared with women who were never exposed to active and passive smoking, former smokers and current smokers had odds ratios of 1.15 and 1.47 (table 2), and those who were ever active smokers had an odds ratio of 1.31 (95 percent confidence interval (CI): 0.90, 1.92). The odds ratio was 1.61 for only passive exposure. A comparison of former

TABLE 2. Odds ratios for breast cancer in relation to active tobacco exposure considering passive smoking for participants of a population-based case-control study, Germany, 1992–1995

	Cases (n = 468)		Controls (n = 1,093)		OR*,†	95% CI*
	No.	%	No.	%		
Unexposed to active and passive smoking	44	9.4	144	13.2	1.00	
Ever tobacco exposure						
Passive only	153	32.7	310	28.4	1.61	1.08, 2.39
Former active	113	24.1	299	27.3	1.15	0.76, 1.74
Current active	158	33.8	334	30.6	1.47	0.99, 2.20
Missing			6	0.5		
Duration (years) of active smoking‡						
1–9	47	10.0	153	14.0	0.99	0.61, 1.60
10–19	91	19.4	202	18.5	1.40	0.90, 2.16
≥20	133	28.4	278	25.4	1.45	0.96, 2.19
Missing			6	0.5		
					p = 0.047§	
Age (years) at initiation of active smoking‡						
9–15	46	9.8	128	11.7	1.02	0.62, 1.68
16–18	134	28.6	321	29.4	1.29	0.86, 1.94
≥19	91	19.4	184	16.8	1.54	0.99, 2.37
Missing			6	0.5		
					p = 0.015§	
Pack-years of active smoking‡						
≤10	147	31.4	389	35.6	1.19	0.80, 1.76
11–20	81	17.3	141	12.9	1.84	1.17, 2.88
≥21	42	9.0	101	9.2	1.13	0.68, 1.88
Missing	1	0.2	8	0.7		
					p = 0.211§	
Years since cessation of active smoking‡,¶						
1–9	47	15.2	97	12.8	1.64	0.98, 2.75
10–19	40	12.9	128	16.9	0.98	0.59, 1.63
≥20	26	8.4	74	9.7	1.04	0.58, 1.87
Missing			6	0.8		
					p = 0.238§	

* OR, odds ratio; CI, confidence interval.

† Adjusted for average daily alcohol intake, total number of months of breastfeeding, education, first degree family history of breast cancer, menopausal status, and body mass index.

‡ A category of passive smoking only is included in all models.

§ Test for trend excluding passive-only smokers; for years since cessation of smoking, the nonactive/passive smokers were also exluded.

¶ Current smokers excluded from analysis.

smoking and current active smoking with never active smoking, ignoring passive exposure, yielded odds ratios of 0.82 (95 percent CI: 0.61, 1.09) and 1.04 (95 percent CI: 0.80, 1.36), respectively.

The reference category for the following active smoking variables was women who were never exposed to active or passive smoking. There was an increased risk of about 40 percent for smoking 10–19 years and smoking 20 years or more (test for trend excluding passive-only smokers: p = 0.047). After exclusion of current smokers from the analysis, risk estimates decreased with years since cessation from 1.64 for having stopped smoking 1–9 years ago to around unity for 10 or more years. The odds ratios for age at smoking initiation increased from 1.02 to 1.29 to 1.54 for ages 9–15, 16–18, and 19 years or older, respectively (test for trend excluding passive-only smokers: p = 0.015). The risk was significantly elevated for 11–20 pack-years, but it was not increased for more than 20 pack-years.

TABLE 3. Odds ratios for breast cancer in relation to passive tobacco exposure among never active smokers for participants of a population-based case-control study, Germany, 1992–1995

	Cases (n = 197)		Controls (n = 459)		OR*,†	95% CI*
	No.	%	No.	%		
Passive smoke exposure						
No	44	22.3	144	31.4	1.00	
Yes	153	77.7	310	67.5	1.59	1.06, 2.39
Missing			5	1.1		
Passive smoke exposure						
No	44	22.3	144	31.4	1.00	
Former passive‡	92	46.7	191	41.6	1.55	1.00, 2.40
Current passive	61	31.0	119	25.9	1.67	1.04, 2.69
Missing			5	1.1		

* OR, odds ratio; CI, confidence interval.

† Stratified for age in 5-year categories; additionally adjusted for average daily alcohol intake, total number of months of breastfeeding, education, first degree family history of breast cancer, menopausal status, and body mass index.

‡ Former passive smokers have been nonexposed for at least 1 year.

There were 197 cases and 459 controls who had never actively smoked. Of these, 77.7 percent of the cases and 67.5 percent of the controls reported ever having been exposed to tobacco smoke. Ever exposure to environmental tobacco smoke was associated with a 60 percent significantly increased risk (table 3). Unlike for active smoking, there was no difference between former or current passive exposure, when former passive smoking was defined as not having been exposed in the last 10 years (data not shown).

Passive tobacco exposure appeared to have different associations with breast cancer risk, depending on the timing of the exposure (table 4). The odds ratios for exposure only during childhood or only before the first pregnancy were around unity, whereas the odds ratios for exposure only during adulthood or only after the first pregnancy were 1.86 and 2.13, respectively. Analyses regarding the timing of active smoking in relation to the age at first pregnancy show a similar trend, although with somewhat lower odds ratios.

Among nonactive smokers versus the never exposed, an increasing duration in years of environmental tobacco smoke exposure during childhood scarcely altered the risk (odds ratio (OR) = 1.51, 95 percent CI: 0.78, 2.95 for 1–10 years of exposure; OR = 1.45, 95 percent CI: 0.92, 2.29 for 11 years or more) (table 5). For exposure during adulthood, the odds ratio was statistically significant for 1–10 years (OR = 1.85, 95 percent CI: 1.15, 2.98) and decreased somewhat for 11–20 years and 21 years or more (ORs = 1.59 and 1.51, respectively). Adjusting for the duration of adulthood exposure when examining the effect of the duration during childhood and reciprocally adjusting for the duration of childhood exposure when examining the effect of the duration during adulthood did not substantially alter these estimates (data not shown). Considering intensity and duration of exposure together yielded an increased risk for 1–50 hours/day-years and a significantly increased risk for 51 or more hours/day-years (test for trend: $p = 0.009$).

To evaluate the joint effects of active and passive smoke, we constructed six groups of women with different combinations of exposures, taking into consideration the duration and intensity of exposure (table 6). The odds ratios were significantly increased for women who were only passively exposed (OR = 1.57) and those who had both high passive and high active exposures (OR = 1.78). The risk estimates for women with the other four combinations of exposures were around unity. Low or high passive exposure among nonactive smokers was associated with similar odds ratios, whereas among active smokers the odds ratios were 1.06 for low and 1.46 for high passive exposure.

DISCUSSION

This study supports the hypothesis that active and passive smoke exposures are associated with an increase in breast cancer risk. Ever active smoking increased the risk by about 30 percent, current active smoking by about 50 percent, and ever passive smoking by about 60 percent. The greatest increase in risk of 80 percent was found for those who had both high active and high passive exposures. These risks are lower than the risks in recent studies where risk estimates were about 2 for both active and passive smoking (15, 16, 18–21). Neglecting passive smoke in the analysis gave odds ratios consistent with the past body of literature that considered only active smoking.

Active smoking

Data on active smoking variables such as duration, age at initiation of smoking, and years since cessation were reported by five recent studies that had also considered passive smoking (18, 20, 21, 26, 27), with two assessing passive exposure only in adulthood and focusing on gene-environment interactions with polymorphisms in *NAT1* and

TABLE 4. Odds ratios for breast cancer in relation to timing of active and passive tobacco exposure for participants of a population-based case-control study, Germany, 1992–1995

	Cases		Controls		OR*,†	95% CI*
	No.	%	No.	%		
Timing in life						
Passive smoke exposure‡,§						
Never	44	22.3	144	31.4	1.00	
Passive only as child	14	7.1	44	9.6	1.11	0.55, 2.27
Passive only as adult	65	33.0	113	24.6	1.86	1.16, 2.98
Passive as child and adult	74	37.6	153	33.3	1.63	1.03, 2.57
Missing			5	1.1		
Timing in relation to pregnancy¶						
Passive smoke exposure‡,#						
Never passive	37	21.9	114	30.4	1.00	
Passive before first pregnancy	28	16.6	78	20.5	1.13	0.63, 2.04
Passive after first pregnancy	16	9.5	23	6.1	2.13	0.98, 4.60
Passive before and after	88	52.1	160	42.1	1.56	0.97, 2.50
Missing			5	1.3		
Active smoke exposure**,††						
Never active/passive	37	9.6	114	12.9	1.00	
Active before first pregnancy	27	7.0	94	10.6	0.92	0.52, 1.65
Active after first pregnancy	30	7.8	57	6.4	1.64	0.90, 2.97
Active before and after	159	41.3	355	40.0	1.32	0.86, 2.03
Missing			5	0.6		

* OR, odds ratio; CI, confidence interval.

† Stratified for age in 5-year categories; adjusted for average daily alcohol intake, total number of months of breastfeeding, education, first degree family history of breast cancer, menopausal status, and body mass index.

‡ Ever active smokers are excluded from analysis.

§ Cases: $n = 197$; controls: $n = 459$.

¶ Only parous women.

Cases: $n = 169$; controls: $n = 380$.

** Only passive smoking included in model.

†† Cases: $n = 385$; controls: $n = 887$.

NAT2 (26, 27). However, in some studies, adjustment was not made for passive smoking in the results presented (18, 26, 27). An increase in risk for a longer duration of smoking was not found in the above studies. Our finding of a significantly increased risk for 11–20 pack-years of cigarettes smoked and then a decreased risk for more than 20 pack-years is compatible with two previous findings (20, 21). This could nevertheless be a chance finding pertaining to small numbers. A consistent increase in breast cancer risk for every category of number of daily cigarettes and of pack-years was reported in only one study (19). The increasing risk for increasing age at initiation of smoking found in this study has not been found in previous reports; either no association or no changing effect on risk with changing age was seen (18, 20, 21, 26, 27).

Passive smoking

Ever passive smoking was defined to be more than 1 hour per day of exposure for at least 1 year in either childhood or adulthood. All the analyses redone with usage of a strict yes/no definition of ever passive exposure did not essentially alter the estimates. Passive smoking significantly elevated breast cancer risk among never active smokers. However, there was no difference in risk between former and current passive exposures or between high and low passive exposures. Previous reports have not presented data that can be compared.

In relation to the timing of passive exposure among never active smokers, there was no effect on breast cancer risks for exposure only during childhood or only before the first pregnancy, but there was an increased risk for exposure in adulthood or after the first pregnancy. Johnson et al. (21) also found the risk for childhood exposure to be lower than that for adulthood exposure, and Smith et al. (18) reported similar findings, albeit with large confidence intervals including unity. Lash and Aschengrau (20) reported similar odds ratios for exposure during adulthood and during childhood. Contrary to the assumption that breast tissue is most susceptible to carcinogens at young ages, early passive smoking may not play an important role in breast carcinogenesis. Although misclassification may be high for child-

TABLE 5. Odds ratios for breast cancer in relation to duration in years and to hours/day-years of passive tobacco exposure for nonactively smoking participants of a population-based case-control study, Germany, 1992–1995

	No. of cases (n = 197)	No. of controls (n = 459)	OR*,†	95% CI*
Never passive (referent)	44	144	1.00	
Passive smoke exposure in childhood (≤18 years)				
1–10 years	20	43	1.51	0.78, 2.95
≥11 years	68	154	1.45	0.92, 2.29
Passive only as adult	65	113	1.80	1.12, 2.89
Missing		5		
Passive smoke exposure in adulthood (>18 years)				
1–10 years	61	109	1.85	1.15, 2.98
11–20 years	35	70	1.59	0.91, 2.75
≥21 years	43	87	1.51	0.89, 2.56
Passive only as child	14	44	1.07	0.52, 2.19
Missing		5		
Passive exposure in lifetime‡				
1–50 hours/day-years	64	149	1.42	0.90, 2.26
≥51 hours/day-years	88	153	1.83	1.16, 2.87
Missing	1	13		
				p = 0.009§

* OR, odds ratio; CI, confidence interval.

† Stratified for age in 5-year categories; adjusted for average daily alcohol intake, total number of months of breastfeeding, education, first degree family history of breast cancer, menopausal status, and body mass index.

‡ Among nonactive smokers: sum of hours/day-years for the sources partner, work, and childhood, whereby childhood hours/day-years were divided by the number of smokers to avoid overlapping of exposures.

§ Test for trend.

hood exposure, studies on the association of lung cancer and environmental tobacco smoke are fairly consistent in reporting that childhood exposure does not affect lung cancer risk (28).

The duration of lifetime passive exposure in never active smokers was not associated with an increase in risk with increasing duration, as also reported by Lash and Aschengrau (20). Johnson et al. (21) saw an increasing risk with increasing duration, especially when multiplying the duration by the intensity of the number of exposed smokers. We found that risks increased with lifetime hours/day-years of exposure, whereas in a similar analysis, Morabia et al. (19) saw no difference in risk between 1–50 and more than 50 hours/day-years.

Joint effects

Previous studies have not evaluated the joint effects of different exposures of active and passive smoke considering duration and intensity. In this study, only passive exposure and the combination of high passive and high active exposures yielded significantly increased risks, whereas the other combinations had risks around unity.

Biologic plausibility

A biologic explanation of how active and passive tobacco exposures affect breast cancer risk remains unclear. Differences in conditions during smoke formation were found to contribute to a remarkable discrepancy of physicochemical compositions between mainstream smoke and sidestream smoke (29). Sidestream smoke contains higher concentrations of many components, such as volatile *N*-nitrosamines, tar, carbon monoxide, carbon dioxide, benzene, ammonia, nicotine, and benzo[*a*]pryene (29, 30). The vapor-phase constituents absorb more quickly into blood and lymph systems than do particulate-phase constituents that are predominantly found in mainstream smoke, making an effect of passive smoke on breast carcinogenesis plausible (17).

Active smoke has been associated with an antiestrogenic effect (2, 7, 8), which may be balanced by direct carcinogenic damage in the breast tissue (11, 12). It is possible that passive smoking among nonsmokers may have a deleterious effect if the direct carcinogenic damage in the breast tissue outbalances the antiestrogenic effect due to higher concentrations of tobacco-related carcinogens, specifically from higher concentrations of vapor-phase constituents. These possibilities are corroborated by a recent paper reporting that a reduced age at menopause was related to current active, but not to passive or former active, smoking (31). This suggests

TABLE 6. Odds ratios for breast cancer for combinations of active and passive tobacco exposures for participants of a population-based case-control study, Germany, 1992–1995

	Cases		Controls		OR*,†	95% CI*
	No.	%	No.	%		
Never active/passive (referent)	44	9.5	144	13.3	1.00	
All‡						
Only passive	153	33.0	310	28.6	1.57	1.06, 2.35
Only active	27	5.8	81	7.5	1.12	0.64, 1.97
Low passive/low active§	40	8.6	137	12.6	0.98	0.60, 1.61
High passive/low active§	38	8.2	114	10.5	1.05	0.63, 1.74
Low passive/high active§	44	9.5	100	9.2	1.28	0.77, 2.11
High passive/high active§	118	25.4	198	18.3	1.78	1.16, 2.71
Missing	4		9			
Nonactive smokers						
Low passive	91		188		1.69	1.10, 2.59
High passive	61		114		1.69	1.05, 2.73
Missing	1		13			
Active smokers						
Only active	27		81		1.11	0.63, 1.96
Low passive	84		237		1.06	0.69, 1.64
High passive	156		311		1.46	0.97, 2.18
Missing	4		5			

* OR, odds ratio; CI, confidence interval.

† Stratified for age in 5-year categories; adjusted for average daily alcohol intake, total number of months of breastfeeding, education, first degree family history of breast cancer, menopausal status, and body mass index.

‡ The following categories were included in one model.

§ Low active exposure: <7 pack-years; high active: ≥7 pack-years; low passive exposure: <75 hours/day-years; high passive: ≥75 hours/day-years.

that there is little or no antiestrogenic effect of passive smoking, in contrast to current active smoking.

Active smokers are exposed to their own generated smoke, which makes it necessary also to regard active smokers as passively exposed. The analysis of joint exposures was an attempt to separate the effects of different levels of tobacco exposure. The results on joint effects point to the importance of the balance between adverse and protective effects at different levels of intake and between active and passive smoking. It is therefore conceivable that low active smoking is associated with an overall beneficial antiestrogenic effect, while for high active smoking this effect is outweighed by direct carcinogenic effects, particularly when coupled with high passive exposure.

Bias and reliability

The results presented here are of a lower magnitude but, consistent with those reported from several previous studies, they point in the same direction. However, it is possible that selection bias may have affected our findings, particularly because in this study women were recontacted for information regarding passive smoke exposure and because those who had died since the first interview could not be included. Regarding known breast cancer risk factors, the original study population seemed representative (24), and the distribution of all examined variables, most importantly the daily number of cigarettes reported in the first questionnaire, did not appreciably differ between the original and the new study populations. A selection regarding passive exposure cannot be ruled out because environmental tobacco smoke was not assessed before. Nonetheless, a recent report indicated that passive smoking is not associated with breast cancer mortality (22) so that survival bias may well be negligible. Persons who refused participation are unlikely to differ in their environmental tobacco smoke exposure when all other variables, including active smoking, seem similarly distributed. A comparison between prevalences of female controls of a German case-control study on environmental tobacco smoke and lung cancer and those of the present study shows a good concordance for ever passive smoking (69 percent vs. 68 percent), for ever exposed to spousal smoking (59 percent vs. 53 percent), and for ever exposed at work (52 percent vs. 55 percent) (32).

Cases and controls may recall their active and passive tobacco exposures differently. There was no great change in recall for active smoking between the first questionnaire and the second interview even though smoking was only a minor aspect in the first study. Taking into account the good quality of the other assessed factors, it seems unlikely that the

reporting of active or passive exposure should be greatly biased by case-control status.

Studies on the reliability of lifetime passive smoking data are rare, but generally it seems that the validity of self-reports of passive smoking is good but declines with increasing requests for details or quantifications (33). In two validation studies of lung cancer patients and controls on lifetime passive smoking, the concordance of responses between interviews about 2 years apart was relatively high (34), and reports of next of kin corresponded well with self-reports (35).

Conclusion

This study strengthens the accumulated evidence of an increase in breast cancer risk associated with active and passive exposure. The results of the joint exposure analysis indicate that active and passive smoking should not only be examined separately but also in combination. These findings are of a high priority for public health recommendations, because the prevalences of passive smoking are high and because active smoking prevalences among German adolescents are growing (36).

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