**INTERNATIONAL RESEARCH PROMOTION COUNCIL**

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# World Scientists Forum International Awards

in

## Cancer Epidemiology and Clinical Research

## EMINENT SCIENTIST OF THE YEAR 2006

EUROPE

## INGER T. GRAM, M.D., PH.D.

NORWAY

# EMINENT SCIENTIST OF THE YEAR 2006

## EUROPE



Inger T. Gram, M.D., Ph.D.

*Prof. Inger Torhild Gram, a world renowned Cancer Epidemiologist and expert in Clinical Research is currently working as Professor and Head of the Department of Preventive Medicine, Institute of Community Medicine, Faculty of Medicine at the University of Tromsø, Norway and Medical Officer at the University Hospital of North Norway, Tromsø, Norway.*

*Prof. Gram received her M.D. and Ph.D. degrees from the University of Tromsø. She spent two years as Visiting Scientist at the Department of Epidemiology, University of Alabama at Birmingham, School of Public Health and one year at the Department of Preventive Medicine, School of Medicine, University of Southern California, Los Angeles, prior to becoming Professor in Epidemiology and Medical Statistics at the University of Tromsø in 1999.*

*Prof. Gram was the first female physician with medical training from the University of Tromsø who was appointed a full professor. Her collaborative efforts in cancer epidemiology has also resulted in one year as Visiting Scientist at the International Agency of Cancer Research, Lyon, France/the Cancer Research Center of Hawaii, University of Hawaii, Honolulu. Hawaii, USA. The experience she gained from working at different institutions and with colleagues from all over the world was of a valuable help to her. She has two children who also shared the valuable experience of living in other countries with her. She received several honors and awards.*

*Prof. Gram's contribution to the etiology of smoking related cancers started with her thesis work which included one of the first follow-up studies on smoking and cervical cancer. As a result of this work, she is now a member of the "International Collaboration of Epidemiological Studies of Cervical Cancer": with researchers from both the developed and the developing countries. Prof. Gram is still continuing her work in cancer epidemiology in the "Norwegian Woman and Cancer Study", where she leads the work concerning smoking related cancers. Prof. Gram is also working with cancer epidemiology and especially with smoking related cancers in the "European Investigation into Cancer and Nutrition including men and*

*women from ten European countries. She is also the P.I. of the "Mammography and Breast Cancer Study", a study utilizing mammographic densities as a surrogate endpoint for breast cancer. This study has also resulted in international collaborative efforts.*

*Prof. Gram's skills in the area of cancer epidemiology have resulted in extensive research based teaching in both the School of Medicine and in the Master of Public Health program at the University of Tromsø.*

*Prof. Gram is interested in public health implications of her scientific knowledge. She has therefore chaired the different appointed working groups leading to the implementation of a "Smokefree work environment at the University of Tromsø" (1995), implementing "Smokefree premises inside the University Hospital of North Norway" (1997) as of January 1st, 1997, and "Smokefree employees during working hours" (2003). Prof. Gram has also served seven years at the Advisory Board of the National Council on Tobacco and Health, Norway. She has also given interviews in national newspapers, radio and TV concerning cancer epidemiology and have given invited talks in countries all over the world.*

*Prof. Gram is of the opinion that it is very important to collaborate across boarders in cancer epidemiology and preventive medicine. It is a huge challenge to implement the knowledge in cancer epidemiology and preventive medicine in the developing and underdeveloped countries.*

*Prof. Gram's research interests are in Etiology and prevention of cancer; cancer epidemiology, cancer biology, early detection, tobacco epidemiology, gene-environment interactions in cancer, female cancers, tobacco control, screening programs, public health implications.*

*Prof. Inger Torhild Gram has been selected by the World Scientists Forum for "Eminent Scientist of the Year 2006" International Award in the field of 'Cancer Epidemiology and Clinical Research' from the Scandinavian Countries based on her unique research contributions, innovative ideas and actions against smoking and especially her management and organisational skills.*



THE UNIVERSITY OF TROMSØ, NORWAY
– THE WORLD'S NORTHERNMOST UNIVERSITY

The University of Tromsø with its 7000 students is the northernmost University in the world. Opened in 1972 it has been largely responsible for giving the city an international flavor, with people from over 120 different countries living here. The School of Medicine is located in the Health Sciences Building adjacent to the University Hospital of North Norway. The University Campus is approximately 4 km north of downtown Tromsø.

Located above the Arctic Circle close to 70° Northern latitude, the city and island of Tromsø lies in the province of Northern Norway, which is made up of the 3 most northern counties in Norway. The area of the province is equal to 1/3 of the total land area of Norway but only has a population of 460.000, which is equivalent to 11% of the total population.

The Midnight Sun can be observed for two months from

the middle of May. Correspondingly, there are two months of Winter Darkness when the sun is always below the horizon from mid November. During the winter months the spectacular aurora borealis (northern lights) can be observed. In spite of a location corresponding to Northern Alaska, the mean temperature in July is 12 °C, thanks to the Gulf Stream, which even keeps the fjords from freezing during winter.

The University of Tromsø is owned by the State and receives its grants directly from the State Budget. The University's highest organ is the University Board. Professor Jarle Aarbakke, MD, Ph.D, is the Rector and the University's chief representative. He was recently re-elected for a period of another three year period.

The University of Tromsø is a vital source of research and education at the intersection between the Polar region's unique challenges - and the Cornucopia of learning. The region is distinguished by its abundance of natural resources, polar proximity, multi-cultural communities, scattered population, and major export industries. In a world where research and education are subject to an ever-increasing internationalisation the University of Tromsø has a global perspective, open to external influence and inspiration.

## A BRIEF HISTORY OF THE UNIVERSITY OF TROMSØ, NORWAY:

**1918:** The wholesaler Hans A. Meyer, puts forward the idea of a University in Tromsø

**1968:** Parliament approves the establishment of the University of Tromsø on March 28th

**1972:** The University is officially opened by King Olav V and the first students are enrolled.

**1978:** The University moves into its first permanent buildings in Breivika

**1988:** The Norwegian College of Fishery Science is established at the University of Tromsø

**1989:** The University establishes the Centre for Environment and Development studies.

**1990** The University establishes the Centre for Saami Studies.

**1991:** The Medical and Health Studies' building and Tromsø Regional Hospital are opened

**1993:** The University of Tromsø celebrates its 25th. Anniversary - student enrolment 6,000

**1994:** The Norwegian College of Fishery Science building in Breivika is inaugurated

**1995** The University establishes the Centre for women's research and women in research

**1997:** The University introduces a faculty-based organisational structure

**1998:** The University of Tromsø celebrates its 30th. Anniversary.

**2002:** The University establishes the Centre for Peace Studies.

**2003:** The University establishes the Centre for International Health

# Breast Cancer Risk Among Women Who Start Smoking As Teenagers

[1,2]Inger T. Gram, M.D., Ph.D., [1]Tonje Braaten, M.Sc., [3]Paul D. Terry, Ph.D., [4,5]Annie J. Sasco, M.D. Dr P.H., [6]Hans-Olov Adami, M.D., Ph.D., [1]Eiliv Lund, M.D., Ph.D., [6,7]Elisabete Weiderpass, M.D., Ph.D.

[1]Institute of Community Medicine, University of Tromsø, Breivika N-9037 Norway
[2] University Hospital North –Norway, Tromsø, Breivika N-9038 Norway
[3] NIEHS, Epidemiology Branch P.O. Box 12233 MD A3-05, Research Triangle Park, NC 27709- 2233, USA
[4]International Agency for Research on Cancer, 150 cours Albert Thomas, 69008 Lyon, France
[5]Institut National de la Santé et de la Recherche Médicale, Lyon, France
[6] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-17176 Stockholm, Sweden
[7] Cancer Registry of Norway, Montebello, N-0310 Oslo, Norway

## ABSTRACT

***Objective:*** *To examine the effect of smoking on breast cancer risk in a large population-based cohort of women, many of which started smoking as teenagers.*

***Methods:*** *We followed 102,098 women, aged 30-50 years, completing a mailed questionnaire at recruitment to the Norwegian-Swedish Cohort Study in 1991/1992, through December 2000. We used Cox proportional hazard regression models to estimate relative risk (RR) of breast cancer associated with different measures of smoking initiation, duration and intensity adjusting for confounding variables. We conducted analyses on the entire study population n, among women who had smoked for at least 20 years, among non-drinkers, and separately for each country.*

***Results:*** *Altogether 1,240 women were diagnosed with incident, invasive breast cancer. Compared with never smokers, women who smoked for at least 20 years and who smoked 10 cigarettes or more daily had a RR of 1.34 (95 % confidence interval (CI) 1.06 - 1.70). Likewise, those who initiated smoking prior to their first birth (1.27, 1.00 - 1.62), before menarche (1.39, 1.03 - 1.87), or before age 15 (1.48, 1.03 - 2.13) had an increased risk. In contrast, women who had smoked for at least 20 years, but started after their first birth did not experience an increased breast cancer risk. The increased RR associated with smoking was observed among non-drinkers of alcohol, women with and without a family history of breast cancer, pre and postmenopausal women, and in both countries.*

***Conclusion:*** *Our results support the notion that women who start smoking as teenagers and continue to smoke for at least twenty years may increase their breast cancer risk.*

**Keywords:** *Smoking, breast cancer, incidence, cohort, teenager, age at first birth, alcohol, risk factors, epidemiology, women, Norway, Sweden*

Correspondence to: Dr. Inger Gram, Institute of Community Medicine, University of Tromsø, N-9037 Tromsø, Norway
Tel.: +47 77 64 48 16 Fax: +47 77 64 48 31. e-mail: inger.gram@ism.uit.no

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## INTRODUCTION

The relationship between smoking and the risk of breast cancer has been unclear for several decades, and whether or not young women should be warned about smoking as a possible cause of breast cancer remains controversial.[1-4] In 1982, MacMahon and colleagues first suggested a protective effect[5] while Hiatt & Fireman four years later proposed a detrimental effect of smoking on breast cancer risk (6). Since then, studies have continued to show positive, inverse, or null associations.[4,7-9]

In 2002, a pooled analysis of 53 epidemiological studies found that the positive relationship between smoking and breast cancer was likely due to confounding by alcohol consumption, an established cause of breast cancer.[10] However, this study used crude smoking measures, e.g. ever versus never smokers and also including passive smokers in the reference group, possibly diluting a weak effect. From a public health perspective, even a small increase in the risk of breast cancer among women who smoke may account for a substantial number of cancer cases in populations where the prevalence of smoking is high.

Russo and colleagues[11] hypothesized in 1982, that the mammary tissue is particularly susceptible to carcinogenic exposures during the years from pre-puberty to the first birth, when the mammary cells differentiate. Therefore, we examined the association between cigarette smoking and breast cancer risk in a large population-based cohort of women who were teenagers when smoking prevalence increased markedly among young Scandinavian women.

## MATERIALS AND METHODS

### Study population

The Norwegian-Swedish Women's Lifestyle and Health Cohort Study was initiated in 1991/1992. In Norway, a nationwide random sample of 100,000 women, born between 1943 and 1957, was drawn from the National Population Register at Statistics Norway. In Sweden, a random sample of 96,000 women, born between 1943 and 1962 residing in the Uppsala Health Care Region, was drawn from the National Population Register at Statistics Sweden.

All women received a letter inviting them to participate in the study. The letter requested that they provide written informed consent, and contained a comprehensive questionnaire that was to be completed and returned in a prestamped envelope. The common set of questions included detailed assessment of smoking habits, alcohol consumption, contraceptive use, reproductive history, history of breast cancer in the mother and sister(s), height and current weight (allowing us to calculate body-mass-index (BMI) as weight in kilograms divided by the square of height in meters), and other aspects of lifestyle habits. In both countries the national Data Inspection Boards and the regional Medical Ethical Committees approved the study. All women gave written informed consent to participate.

### Smoking Assessment

The questionnaire elicited information on current and previous smoking history, and asked if the women lived with a smoker or had done so during childhood. We categorized women who had never smoked, but been exposed to passive smoke at home as 'passive smokers' and those reporting neither as 'never smokers'.

We categorized the ever-active smokers according to current and past smoking status, smoking duration; number of cigarettes smoked daily, pack-years of smoking (i.e. number of cigarettes smoked per day, divided by 20, multiplied by the number of years smoked), and years of smoking latency (i.e., age at cohort enrollment minus age of smoking initiation). We further separated them into three descriptors of timing of smoking initiation: 1) age started smoking whether they started smoking 2) before or around menarche, and 3) before their first birth.

We classified women who had smoked for at least 20 years as long-term smokers, and calculated their average smoking duration, according to the three descriptors of timing of smoking initiation. We categorized past smokers according to smoking recency, i.e. years since they stopped smoking.

### Other Exposures

Women who reported a natural menopause or a bilateral oophorectomy at cohort enrollment were considered post-menopausal, regardless of age at hysterectomy, or use of hormone replacement therapy. Women were classified as post-menopausal when they reached 50 years of age during follow-up. We calculated average daily consumption of alcohol in grams based on the content of pure alcohol in the different sorts of beverages among drinkers. Women who reported to be teetotalers, and those answering 'seldom or never' in the frequency table, are from heron referred to as non-drinkers. Their alcohol consumption was set to 0.

### Follow-up

In Norway, 57,584 (57.6 %) and in Sweden 49,259 (51.3%) women returned completed questionnaires, resulting in an overall response rate of 54.5. The cohort data were linked

to the national registries of cancer and statistics in Norway and Sweden, to identify all incident cancer cases and deaths/ emigrations, respectively. Woman-years were calculated from the start of follow-up to the date of diagnosis of primary invasive breast cancer, the date of emigration, death, or the end of follow-up, i.e., December 31, 2000, whichever occurred first.

Among the 106,841 women included, 789 emigrated and 1,360 died during follow-up. We excluded five women due to missing vital status information (whether they were alive, dead or emigrated) in the available register files, 15 women who had emigrated or died before the start of follow-up, and 1,681 women who were diagnosed with any invasive cancer prior to the start of follow-up for a total of 1,701. We excluded 3,042 women with no information on smoking history, leaving 102,098 subjects in the analytical cohort.

## Statistical Analysis

We obtained crude breast cancer incidence rates by dividing the number of cases by the total number of woman-years in that exposure category. The rates were then age-adjusted to the world standard population.[12] We estimated RRs of breast cancer associated with different measures of smoking exposure as described by Cox.[13] We tested for trends across categories of smoking variables by assigning equally spaced scores to the categories and treating the variable as continuous in the analyses. The trend test analyses did not include passive smokers. Unless otherwise specified, the reference group is never smokers throughout the paper.

Potential confounding variables for the smoking and breast cancer association were examined and, those of importance i.e. age at enrollment, age at menarche, age at first birth, number of children, menopausal status, family history of breast cancer, hormonal contraceptive (HC) use, consumption of alcohol, and BMI, were included in the final models. Age at first birth (<21, 21-24, 25 +) and parity (0,1,2,3+) were considered as a set of indicator variables. The multivariate analyses presented here are based on 91,125 women with information on the above listed variables. We repeated all analyses excluding 60 women diagnosed with breast cancer during the first 12 months of follow-up. The RR estimates obtained in this way were not materially different from the results presented in the paper (data not shown).

We conducted analyses on the entire study population, among long-term ever smokers, among non-drinkers, and separately for each country. We also compared the RR of breast cancer among long-term smokers stratified by country and by two (high/low risk) categories of established breast cancer risk factors. Subsequently, we conducted analyses including passive smokers in the reference group. Since smoking influence BMI and age at menopause, we also conducted analyses excluding BMI and age at menopause from the models, one by one, and both at the same time, as well as setting menopause at 54/52 years for never/current smokers.

We did the Cox proportional hazards analyses with the PHREG procedure in the SAS statistical package[14] We entered multiplicative terms between smoking and possible effect modifiers in the proportional hazards model to evaluate interaction, and tested for heterogeneity between strata with Wald chi-square statistics. RRs are given with 95% CIs. Results were considered as statistically significant if the P value was 0.05 or less, and 95% CIs are reported throughout the paper. All P values are two-sided.

## RESULTS

During the 924,768 person-years of observation, 1,240 incident cases of primary invasive breast cancer, confirmed by histology, were identified. Altogether 64 % of the women reported to be ever smokers, while 13 % were classified as never smokers. Table 1 shows that Norwegian women were more likely to be past or current smokers than Swedish women (P <0.001).

Table 2 shows that the distribution of selected characteristics varies according to smoking status. Current smokers differ from past smokers on all the listed variables in the table (all P -values <0.001), but for family history of breast cancer (P =0.77). The table displays that current and passive smokers also differ significantly from never smokers on most of the selected characteristics.

At enrollment, more than half of the past smokers had quit smoking five or more years ago. All the measures of smoking exposure i.e. time of smoking initiation, smoking intensity, and duration, differ between current and past smokers in the cohort (all P -values <0.001). Altogether 51% among current and 63% among past smokers reported to be light smokers i.e. smoke less than 10 cigarettes per day. Among non-drinkers, 49% among current and 60 % among past smokers reported to be light smokers. Among current smokers, 69% of the non-drinking and 70% of all women reported to be long-term smokers (P =0.34).

The age-adjusted incidence rates of breast cancer were 114 per 100,000 woman-years among never smokers, 120 among past-smokers, and 135 among current smokers. The corresponding rate among women who had been exposed to passive smoking at home was 134 per 100,000 woman-

**Table 1. Selected characteristics of the participants (N=102, 098) in the Norwegian-Swedish Cohort Study, 1991-2000.**

| Characteristics | Norway | Sweden | Total |
|---|---|---|---|
| Age at enrollment, median (range) | 41 (34-50) | 40 (30-50) | 40 (30-50) |
| Number of women | 54321 | 47777 | 102098 |
| Person-years of follow-up | 493832 | 430936 | 924768 |
| Median follow-up time in years | 9.6 | 9.3 | 9.3 |
| Number of invasive breast cancers (BC)[a] | 693 | 547 | 1240 |
| Crude BC incidence rate[b] | 140 | 127 | 134 |
| Age adjusted BC incidence rate[c] | 131 | 127 | 127 |
| Age at BC diagnosis, median (range) | 48 (36-57) | 49 (30-58) | 48 (30-58) |
| **Smoking status at cohort enrollment**[d] | | | |
| Current (%) | 29.3 | 26.6 | 28.0 |
| Past (%) | 38.8 | 32.7 | 36.0 |
| Passive (%)[e] | 22.9 | 24.2 | 23.5 |
| Never (%) | 9.0 | 16.5 | 12.5 |

[a] Incident cases of breast cancer during follow-up through 2000.
[b] Number of incident cases per 100, 000 woman-years.
[c] Per 100 000 woman-years, adjusted to World Standard population.
[d] Chi-square test for differences between Sweden and Norway, P <0.001
[e] Women who never smoked, but living with smokers during childhood or at cohort enrollment.

**Table 2. Distribution of selected characteristics of study population (N=102,098) at cohort enrollment, given as mean (± s.d.) and (%), by smoking status, Norwegian-Swedish Cohort Study, 1991-2000.**

| Characteristics | Current smokers (N=28,624) | Past smokers (N=36,701) | Passive smokers (N=24,030) | Never smokers (N=12,743) | p Value[a] |
|---|---|---|---|---|---|
| Age (years) | 40.5±5.0 | 40.1±4.9[b] | 40.6±5.2[c] | 40.1±5.5 | <0.001 |
| Age at diagnosis (years) | 48.6±5.2 | 47.4±5.2[b] | 48.0±5.4 | 47.9±5.5 | 0.04 |
| Education (years) | 11.4±2.9 | 12.1±3.1[b] | 12.6±3.2[c] | 13.2±3.2 | <0.001 |
| Age at menarche (years) | 13.1±1.4 | 13.1±1.3[b] | 13.1±1.4 | 13.1±1.3 | 0.98 |
| Post-menopausal (%) | 7.2 | 4.2[b] | 4.3[c] | 3.6 | <0.001 |
| Age at menopause (years) | 42.4±4.7 | 41.9±4.7[b] | 42.8±4.7 | 43.0±4.3 | 0.09 |
| Family history of breast cancer(%)[d] | 4.9 | 4.8 | 4.9 | 4.9 | 0.41 |
| Parous (%) | 87.9 | 90.0[b] | 88.0[c] | 84.9 | 0.001 |
| Age at first birth (years) | 22.9±4.2 | 24.0±4.4[b] | 24.5±4.2[c] | 25.4±4.2 | 0.001 |
| No of children | 2.0±1.1 | 2.0±1.1[b] | 2.1±1.1[c] | 2.0±1.2 | 0.001 |
| Ever Hormonal Contraceptive use (%) | 76.7 | 76.8[b] | 68.3[c] | 65.4 | <0.001 |
| Teetotallers (%) | 15.0 | 16.7[b] | 25.1[c] | 33.0 | <0.001 |
| Alcohol consumption g/day[e] | 4.6±6.5 | 4.2±5.6[b] | 3.3±4.2[c] | 2.9±3.6 | <0.001 |
| Mean Physical Activity Score[f] | 3.0±0.9 | 3.1±0.9[b] | 3.1±0.9[c] | 3.2±0.9 | <0.001 |
| BMI[g] at enrollment | 23.1±3.5 | 23.2±3.4[b] | 23.5±3.6[c] | 23.0±3.3 | 0.02 |

[a] Chi-square test for differences between current and never smoking groups.
[b] Chi-square test for differences between current and past smoking groups ( p-values <0.001)
[c] Chi-square test for differences between passive and never smoking groups ( p-values =<0.01)
[d] Among mother or sister(s).
[e] Among drinkers.
[f] Leisure time physical activity in the year preceding cohort enrollment (scored as 1-5, low to high level.
[g] Body-mass-index; the weight in kilograms divided by the square of the heights in meters).

**Table 3. Multivariate [a] RRs with 95% CI of breast cancer according to various measures of smoking exposures among current and ever smokers smoking at least 20 years compared with never smokers (N=12,743) and the corresponding figures restricted to non-drinkers, with 3, 834 never smokers as reference group, Norwegian-Swedish Cohort Study, 1991-2000.**

| | Study population | | | | Non-Drinkers | | | |
|---|---|---|---|---|---|---|---|---|
| Exposure measures | Current smokers (N=28,624) | | Ever smokers 20+ yrs (N=26,724) | | Current smokers (N=4,043) | | Ever smokers 20+ yrs (N=3,778) | |
| | Multivariate [a] | | Multivariate [a] | | Multivariate [a] | | Multivariate [a] | |
| | Cases (N) | RR [b] (95% CI) | Cases (N) | RR [c] (95% CI) | Cases (N) | RR [d] (95% CI) | Cases (N) | RR [e] (95% CI) |
| Never smokers | 137 | 1.00 (ref.) | 137 | 1.00 (ref.) | 34 | 1.00 (ref.) | 34 | 1.00 (ref.) |
| Smoking initiation | | | | | | | | |
| Age (yrs) | | | | | | | | |
| 20+ | 108 | 1.02 (0.78-1.35) | 84 | 1.16 (0.86-1.57) | 16 | 1.14 (0.59-2.19) | 13 | 1.35 (0.67-2.71) |
| 15-19 | 216 | 1.15 (0.91-1.47) | 259 | 1.23 (0.97-1.55) | 26 | 1.30 (0.72-2.33) | 34 | 1.35 (0.78-2.32) |
| 10-14 | 36 | 1.51 (1.00-2.28) | 49 | 1.48 (1.03-2.13) | 5 | 2.46 (0.90-6.68) | 7 | 2.20 (0.92-5.30) |
| | | P =0.07 [f] | | P =0.03 [f] | | P =0.15 [f] | | P =0.11 [f] |
| Before/around menarche | | | | | | | | |
| No | 282 | 1.10 (0.88-1.38) | 294 | 1.20 (0.96-1.51) | 38 | 1.26 (0.75-2.12) | 41 | 1.37 (0.82-2.29) |
| Yes | 72 | 1.30 (0.94-1.80) | 92 | 1.39 (1.03-1.87) | 7 | 1.52 (0.63-3.66) | 11 | 1.66 (0.79-3.49) |
| | | P =0.13 [f] | | P =0.03 [f] | | P =0.28 [f] | | P =0.13 [f] |
| Before first birth [g] | | | | | | | | |
| No | 91 | 0.99 (0.72-1.37) | 78 | 0.98 (0.70-1.62) | 17 | 1.36 (0.66-2.79) | 12 | 0.97 (0.44-2.12) |
| Yes | 213 | 1.18 (0.92-1.52) | 257 | 1.27 (1.00-1.62) | 26 | 1.46 (0.81-2.64) | 37 | 1.75 (1.02-2.99) |
| | | P =0.14 [f] | | P =0.03 [f] | | P =0.20 [f] | | P =0.03 [f] |
| No of cigarettes per day | | | | | | | | |
| 1-9 | 135 | 0.96 (0.74-1.25) | 138 | 1.10 (0.85-1.43) | 23 | 1.33 (0.74-2.67) | 28 | 1.70 (1.03-3.12) |
| 10+ | 225 | 1.28 (1.01-1.63) | 254 | 1.34 (1.06-1.70) | 24 | 1.25 (0.69-2.26) | 26 | 1.15 (0.65-2.05) |
| | | P =0.03 [f] | | P =0.01 [f] | | P =0.60 [f] | | P =0.89 [f] |
| No of years smoked | | | | | | | | |
| 1-19 | 68 | 0.93 (0.68-1.28) | | - | 10 | 1.07 (0.49-2.32) | | - |
| 20-24 | 96 | 1.09 (0.81-1.45) | 158 | 1.13 (0.88-1.45) | 10 | 0.96 (0.44-2.10) | 22 | 1.32 (0.73-2.38) |
| 25+ | 196 | 1.26 (0.98-1.63) | 234 | 1.36 (1.06-1.74) | 27 | 1.63 (0.90-2.94) | 32 | 1.53 (0.87-2.68) |
| | | P =0.05 [f] | P =0.02 [f] | | | P =0.15 [f] | | P =0.13 [f] |
| No of pack-years | | | | | | | | |
| 0-14 | 162 | 0.95 (0.74-1.20) | 153 | 1.01 (0.85-1.40) | 27 | 1.28 (0.73-2.26) | 29 | 1.61 (0.93-2.78) |
| 15-19 | 90 | 1.28 (0.96-1.72) | 114 | 1.35 (1.02-1.77) | 8 | 1.11 (0.50-2.49) | 12 | 1.26 (0.63-2.53) |
| 20+ | 108 | 1.48 (1.14-1.96) | 125 | 1.46 (1.11-1.93) | 12 | 1.54 (0.72-3.29) | 13 | 1.22 (0.59-2.53) |
| | | P =0.001 [h] | | P <0.02 [h] | | P =0.31 [f] | | P =0.57 [f] |
| Latency (yrs) | | | | | | | | |
| 1-19 | 48 | 0.75 (0.52-1.08) | 12 | 0.88 (0.47-1.66) | 10 | 1.33 (0.62-2.87) | 2 | 1.27 (0.29-5.49) |
| 20-24 | 116 | 1.20 (0.91-1.58) | 125 | 1.13 (0.86-1.47) | 10 | 0.70 (0.30-1.63) | 15 | 1.02 (0.52-2.02) |
| 25+ | 196 | 1.27 (0.98-1.64) | 255 | 1.37 (1.07-1.76) | 27 | 1.67 (0.93-3.02) | 37 | 1.74 (1.01-3.02) |
| | | P =0.02 [h] | | P <0.05 [h] | | P =0.41 [h] | | P =013 [h] |

[a] Adjusted for age at enrollment, menopausal status, number of children, age at first birth, hormonal contraceptive -use, BMI (and alcohol consumption for the analysis among all women).
[b] Based upon a model with 446 cases
[c] Based upon a model with 478 cases
[d] Based upon a model with 74 cases
[e] Based upon a model with 82 cases
[f] Trend test between levels of smoking categories including never smokers.
[g] Among parous women
[h] Trend test between levels of smoking categories excluding never smokers.

years. A multivariate model based on 1,130 cases with complete information on the potential confounders yielded a non-significant increased RR for past 1.15 (95 % CI 0.94 - 1.41), current 1.17 (95 % CI 0.95 - 1.45), and passive 1.21 (95 % CI 0.98 - 1.50) smokers compared with never smokers. An ordinal trend test across three smoking groups (never, past, current) was not statistically significant We also collapsed past and current smokers and used both passive and never smokers as the reference group. This model yielded a RR estimate for ever smokers of 1.0 (95 % CI 0.98 - 1.50). We further examined the association between time since quit smoking among past smokers, and different combinations of childhood and current exposures at home among passive smokers, and breast cancer risk. No meaningful result was revealed (data not shown).

Table 3 shows the RR of breast cancer according to various measures of smoking exposure among current and long-term smokers compared with never smokers. In the analysis including all women, current smokers who began smoking before 15 years of age, those who smoked more than 10 cigarettes a day, or had smoked at least 20 pack-years all had increased risk. Trend tests across the four exposure categories (including the reference group) for number of cigarettes smoked daily (P = 0.03), duration of smoking (P = 0.05), and number of pack-years (P = 0.01) were significant. We observe even stronger associations between smoking and breast cancer risk when the models include only long-term smokers. Those who began smoking before or around menarche had a 39 %, and those starting before their first birth had a 27 % statistically significant increased risk of developing breast cancer. When these models were restricted to non-drinkers, women who started smoking before their first birth, or had a smoking latency period of more than 25 years, presented a significantly increased risk of developing breast cancer of about 75 %. The results among the non-drinkers are based on few cases, and have wide CIEs (Table 3).

We repeated the analyses in Table 3 including passive smokers in the reference group. The associations stayed in the same directions, but became weaker, and only the trend

**Table 4. Multivariate [a] RR estimates for breast cancer with 95% CI based upon 478 cases among women who have smoked for at least 20 years compared with never smokers within two (high/low) risk levels of breast cancer risk factors, Norwegian-Swedish Cohort Study, 1991-2000.**

| Confounding Variables | | Cases N=478 | Multivariate adjusted[a] (95% CI) | P value[b] |
|---|---|---|---|---|
| Age group at enrollment (yrs) | 30-44 | 253 | 1.25 (0.93-1.70) | 0.82 |
| | 45-50 | 225 | 1.19 (0.86-1.65) | |
| Age at menarche (yrs) | <13 | 145 | 0.93 (0.63-1.36) | 0.08 |
| | 13+ | 333 | 1.42 (1.08-1.85) | |
| Menopausal status[c] | Pre | 276 | 1.21 (0.91-1.61) | 0.74 |
| | Post | 198 | 1.31 (0.92-1.88) | |
| Parity | No | 65 | 1.18 (0.68-2.06) | 0.86 |
| | Yes | 413 | 1.25 (0.98-1.58) | |
| Age at first birth (years)[d] | <25 | 255 | 1.31 (0.93-1.85) | 0.59 |
| | 25+ | 158 | 1.15 (0.82-1.61) | |
| Family history of breast cancer in the mother or sisters | No | 432 | 1.23 (0.97-1.55) | 0.82 |
| | Yes | 46 | 1.35 (0.65-2.79) | |
| Hormonal contraceptive use | Ever | 358 | 1.21 (0.93-1.56) | 0.76 |
| | Never | 120 | 1.30 (0.86-1.96) | |
| Body mass index | <=23.9 | 328 | 1.30 (0.99-1.70) | 0.50 |
| | >23.9 | 150 | 1.10 (0.75-1.62) | |
| Consumption of alcohol | Non-drinkers | 82 | 1.43 (0.87-2.33) | 0.50 |
| | Drinkers | 396 | 1.18 (0.92-1.51) | |

[a] Adjusted for age at enrollment, menopausal status, number of children, age at first birth, hormonal contraceptive use, and consumption of alcohol where applicable.
[b] Test for heterogeneity between strata Wald chi-square statistics
[c] Missing numbers due to equivocal menopausal status.
[d] Among parous women

tests for number of pack-years and latency remained statistically significant among current and long-term smokers (all P values <0.05) (data not shown). The risk estimates among *current* smokers displayed in Table 3, with the corresponding trend tests, stayed basically the same when we did country specific analyses, and also when we excluded both the menopausal status and BMI variables from the analyses. Excluding only menopausal status, resulted in weaker dose-response associations, while exclusion of only BMI yielded a stronger association between smoking and breast cancer risk (data not shown). We also obtained stronger associations when we in the multivariate analyses set a different age at menopause during follow-up for never (54 years) and current (52 years) smokers instead of the same age (50 years) for all women. For this model, the trend tests for smoking initiation (age at start (P =0.04); before or around menarche (P =0.08); before first birth (P =0.07), achieved significant or borderline significant results.

Among long-term smokers, those who started before the age of 15 had a 20 % non-significant increased risk when those who started between ages 15 and 19 were the reference group. The former group had on average smoked 1.4 years longer than the comparison group (P =0.001). Likewise, those who started before or around menarche had smoked 1.2 years longer (P =0.001) and had a 15 % increased risk compared to long-term smokers who started after menarche. Similarly, long-term smokers who started before their first birth, had smoked 0.8 years longer (P = 0.001) and had an almost 40 % increased risk when the reference group was those who started smoking after their first birth.

The RR of breast cancer among ever smokers compared with never smokers where the same in Norway and Sweden when stratified by country i.e. 1.24 (95 % CI 0.90 - 1.70). Table 4 shows the RR estimates among long-term smokers compared with never smokers, after stratification by different risk factors for breast cancer. All risk estimates, but for menarche before age 13, were above unity. The test for heterogeneity was not significant for any of the risk factors. The results from Table 4 stayed materially the same when we included passive smokers in the reference group or did country specific analyses (data not shown).

## DISCUSSION

This study finds that women who start smoking prior to menarche or a first birth and continue to smoke for at least twenty years have a small increase in breast cancer risk. A causal interpretation of these results is supported by the presence of a consistent dose-response association between various measures of smoking exposure and breast cancer risk. Furthermore, non-drinkers experience a similar increase in risk as drinkers. Our study shows no evidence that family history of breast cancer; menopausal status or any other established breast cancer risk factor modifies the association with smoking. In contrast, women who have been smoking for twenty years or more, but started after their first birth do not experience an increased breast cancer risk.

Our study has several strengths. The smoking histories were obtained at enrollment and, hence, are not subject to recall bias. We have the ability to separate current and past smokers, and to exclude women exposed to passive smoking at home from the reference group. We have a large proportion of current smokers at enrollment, and have the ability to stratify long-term smokers according to descriptors of smoking initiation, and compare the different groups of long-term smokers. We have detailed information on, and can control for established breast cancer risk factors many of which vary according to smoking status. Additional strengths include the large size of the cohort, that it is sampled from a general population, and has virtually complete follow-up. The cohort shows the expected association between oral contraceptive-use and breast cancer and between HC-use and ovarian cancer.[15,16] We have shown that the study participants are similar to non-participants with respect to several breast cancer risk factors.[17] Furthermore, the cumulated incidence rates during follow-up for all cancer sites as well as for breast cancer sites are almost identical as those reported to the national cancer registry in the same period, suggesting that our findings may be valid in the general population.[18] Indeed, the smoking habits among our Norwegian and Swedish women reflect known smoking patterns in the respective countries.

Our study has several limitations. We have only crude and limited information about passive smoking. Also, since time of smoking initiation and duration are highly correlated, in this relative young cohort, it is very difficult to separate the effects. Furthermore, we do not have updated information on changes in smoking habits, hormonal contraceptive use, hormonal replacement therapy, BMI, menopausal status and alcohol consumption during follow-up, nor lifetime alcohol consumption. However, few Scandinavian women start to smoke after the age of 30, which is the lowest age of enrollment in our study. If current smokers quit smoking during follow-up this may have diluted our results. We already show that by setting the same age at menopause for smokers and never smokers we have biased the displayed results towards the null. In a recent study by Horn-Ross et al.,[19] elevated breast cancer risk was most evident for recent drinking with no clear pattern for consumption during earlier periods of life. The lack of lifetime alcohol consumption in our study may still be a concern. Since the distribution of

established risk factors for breast cancer vary according to smoking status in our cohort, unknown risk factors may do the same. There may be some residual confounding in both directions due to the factors listed above.

Due to smoking trends in Norway and Sweden, women in our cohort have a higher smoking prevalence during their teenage years than women included in the three previous population-based studies from the Scandinavian countries.[20-22] Nevertheless, in our Norwegian-Swedish case-control study including women less than 45 years old at the time of the data collection in 1985, we did find a 30 % non-significant increased breast cancer risk among those who started smoking before 15 years old.[20] Similarly, the Swedish follow-up study, where the youngest women were 18 years old at the time of the data collection in 1963, revealed a 20 % non-significant increased risk among those who began smoking before the age of 19.[22] The Norwegian follow-up study, where the youngest women were 35 years old at enrollment in the mid-1970s, found no association with breast cancer risk.[21]

To date, 13 cohort studies (6;21;23-32) have examined the association between smoking and breast cancer risk. The results of these studies are mixed, but generally show no association. However, the four most recent studies and the only ones including more than 500 breast cancer cases do find a positive association with either long-term smoking,[30] smoking prior to a first birth[29] or both.[31,32]

In contrast to the women in the studies by Egan et al. and Terry et al.,[29,30] our women were aged less than 50 years at enrollment, thus belonging to birth cohorts with different smoking habits than the two North American studies. The most newly published studies[31,32] recruited participants during the 1990's, as we did. However, in the Californian study among teachers[31] there was only 5% and in the Nurses' Health Study II (NHS II) 13 % current smokers at enrollment.[32] In comparison, we have 28 % current smokers in our sample from the general population. This may explain the consistency of our results.

The present study displays a consistent dose-response, which enhances the biologic plausibility of an increased breast cancer risk due to smoking. Plasma lipoproteins may transport the carcinogens in the tobacco smoke to the breast[33] where they can be stored in breast adipose tissue[34,35] and then be metabolized and activated by human mammary epithelial cells. Furthermore, breast tissue of smokers have higher prevalence of smoking-specific DNA adducts and *p53* gene mutations compared with that in non-smokers.[7] This all supports the likelihood of a positive association between cigarette smoking and breast cancer risk. The increased risk associated with smoking prior to a first birth is in accordance with data from epidemiological and animal studies,[7,11,36,37] One important result from our study is that we find no increased risk among women who initiate smoking after a first full time birth. This supports the notion, that breast tissue becomes more resistant to the carcinogens in tobacco smoke after differentiation.

Our study finds that women who start smoking at young ages, and continue to smoke for at least twenty years increase their breast cancer risk. The fact that teenagers who smoke today tend to initiate smoking at earlier ages, than in previous generations, may have implications for targeted efforts to reduce breast cancer risk. Teenage girls and adult women should be given yet another reason to avoid, and to quit smoking.

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Abbreviations used are:
RR = relative risk
CI=confidence interval
BMI= body mass index
HC-use=hormonal contraceptive use.

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