Venous thromboembolism (deep vein thrombosis and/or pulmonary embolism) is the third most common vascular disease and causes large numbers of potentially avoidable deaths. The incidence of venous thromboembolism increases considerably in the first 12 weeks after surgery, with a greater incidence in overweight and obese than in lean patients. Smoking is a well-established risk factor for arterial thrombosis, but the evidence for its role in venous thrombosis is inconsistent, with some reporting a higher risk in current than never-smokers and others reporting no difference in risk. Moreover, few studies have reported on the association between smoking and postoperative venous thromboembolism risk, and those that did have found inconclusive results.

Methods

Study Population

The Million Women Study has been described in detail elsewhere. In brief, this prospective cohort study recruited 1.3 million women through the National Health Service (NHS) Breast Screening Program in England and Scotland between 1996 and 2001 by sending out a recruitment questionnaire (available at www.millionwomenstudy.org) that asked about smoking status and amount currently smoked, as well as use of hormone replacement therapy, height and weight.

In a large prospective study, the Million Women Study, we linked women’s reported smoking history with hospital admission and death records. The aim was to investigate the relationship between smoking and venous thromboembolism risk in the absence of surgery and in the first 12 weeks after surgery. We also examined whether smokers were more likely to undergo surgery than never-smokers, as might be expected given the established relationships between smoking and conditions such as cancer and cardiovascular disease.

Conclusions

Venous thromboembolism incidence was increased in current smokers, both in the absence of surgery and in the 12 weeks after surgery. Smoking is another factor to consider in the assessment of venous thromboembolism risk in patients undergoing surgery.

Key Words: cohort studies • deep vein thrombosis • pulmonary embolism • smoking • surgery
physical activity, alcohol consumption, medical and reproductive history, use of oral contraceptives, education, and other factors.

All study participants are followed up through linkage to NHS Central Registers for deaths, cancer registrations, and emigrations. Additionally, each woman’s unique NHS identification number, together with other personal information, was used to link to cause-specific information on NHS hospital admission databases (including inpatient [ie, overnight] and day-case [ie, not overnight] admissions): Hospital Episodes Statistics for England and Scottish Morbidity Records in Scotland. Information on the date of admission and discharge and on diagnoses and procedures associated with each hospital admission was provided, coded to the World Health Organization’s International Classification of Diseases, 10th Revision (ICD-10) for diagnoses and the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, fourth revision (OPCS-4) for procedures.

Women were classified as having a venous thromboembolism event if they had either a hospital admission record or death registration with an ICD code as listed in the Appendix in the online-only Data Supplement. Women were classed as never, past, or current smokers as reported at recruitment; current smokers were further classified according to the average number (<15, ≥15) of cigarettes smoked per day. Women were classified as having had surgery during follow-up if the hospital data included 1 or more operative codes (see online-only Data Supplement Appendix for nonoperative OPCS-4 codes excluded from this definition).

Statistical Analysis

Women were excluded from the analyses if they reported a history of blood clots or treatment for clotting problems at recruitment, or if, before recruitment, they had a hospital admission for venous thromboembolism (online-only Data Supplement Appendix), had surgery in the previous 12 weeks, or had a previous cancer registration (excluding nonmelanoma skin cancer), or if they had no smoking information at recruitment.

Relative risks (RRs) of undergoing surgery during follow-up and of a venous thromboembolism admission or death (as an inpatient or in the community) according to smoking status at recruitment were estimated from hazard ratios using the Cox regression models, with attained age as the underlying time variable. In the model, age was measured in days and was incremented over time during follow-up so that age at each point in time, rather than age at recruitment, was taken into account in the analyses. The proportional hazards assumption was assessed by use of tests based on Schoenfeld residuals; no evidence of a violation of the assumption was found for any of the analyses. All analyses were adjusted for region of recruitment (10 regions), socioeconomic group (quintiles of Townsend deprivation index), frequency of strenuous exercise (rarely/never, less than or once a week, more than once a week), use of hormone replacement therapy (never, past, current), body mass index (<25, 25–29, 30–34, ≥35 kg/m²), weekly alcohol consumption (<7, 7–13, ≥14 units), history of hypertension, and history of diabetes, as reported at recruitment. For each adjustment variable, an “unknown” category was created to deal with missing values (data missing for ≤5% of women per covariate).

The association between smoking and the risk of venous thromboembolism was explored separately in 2 circumstances: In the absence of surgery and postoperatively in the first 12 weeks after surgery, as described in our previous report. In the analyses of time without surgery, women were followed up from their date of recruitment (or from April 1, 1997, for the 5% of women recruited in England in the year before the Hospital Episode Statistics data were available) and censored at the earliest of the following: Any day or inpatient surgery; cancer registration; emigration, death, or other loss to follow-up in the NHS Central Registers; or the end of hospital record follow-up (the latest date for which complete hospital discharge data were available; March 31, 2008, in England and December 31, 2008, in Scotland). In the analyses related to the postoperative period, women who had at least 1 operation during follow-up were followed up from the date of the first recorded surgery and censored at the earliest of the following: Emigration, death, or other loss to follow-up; the end of hospital record follow-up; or 12 weeks since the first surgery. Operations were classified as day surgery (if admitted and discharged on the same day) or inpatient surgery (at least 1 overnight stay).

STATA version 11.1 was used for all analyses.

Ethical Approval

The Million Women Study was approved by the Cambridge South Research Ethics Committee (formerly Oxford and Anglia Multicenter Research Ethics Committee) and is sponsored by the University of Oxford. Access and linkage to hospital records was approved by the Information Center for Health and Social Care in England and the Information and Statistics Division of the NHS in Scotland. All participants gave written consent for inclusion and follow-up.

Results

A total of 1,162,718 women were included in the present study after the exclusion of 129,274 with previous venous thromboembolism, clotting disorder, cancer, surgery in the 12 weeks before recruitment, or loss to NHS follow-up before study entry and 72,282 who did not report smoking information at recruitment. Table 1 shows the characteristics of these women in relation to smoking status and amount smoked at recruitment. The mean age at recruitment was 56.1 years. Half the cohort had never smoked (51%), whereas 28% were past smokers and 20% were current smokers at recruitment, with similar proportions smoking <15 and ≥15 cigarettes per day. The proportion of women in the lowest socioeconomic tertile increased from 27% in never-smokers to 51% in current heavy smokers. Smokers (past and current) were more likely to be current users of hormone replacement therapy than never-smokers, but current smokers were less likely to exercise regularly or to have a history of hypertension at recruitment.

During 7.28 million person-years of follow-up in the absence of surgery (an average of 6 years of follow-up per woman), 4630 women had a hospital admission with or died of venous thromboembolism. Overall, 636,549 women underwent at least 1 operation during follow-up, and 1852 of these were diagnosed with venous thromboembolism within the first 12 weeks after surgery. The operation was performed as day surgery for 364,482 women, of whom 235 had postoperative venous thromboembolism, and as inpatient surgery for 271,300 women, of whom 1617 had postoperative venous thromboembolism. For a very small number (767), the type of operation was unknown, and no venous thrombosis occurred among them in the 12 weeks after surgery. The most common types of surgery (classified as described previously) were for gastrointestinal (23%), orthopedic (13%), gynecologic (9%), cancer (8%), or vascular disease (7%); each of these conditions was associated with an increased risk of venous thromboembolism in the first 12 postoperative weeks.

Table 2 shows the analyses for risk of venous thromboembolism by smoking status in the absence of surgery. There was a small increase in the risk of venous thromboembolism in past compared with never-smokers (RR 1.08, 95% confidence interval [CI] 1.01–1.16). Current smokers had a 40% greater incidence of venous thromboembolism than never-smokers (RR 1.38 [95% CI 1.28–1.48]). When current smokers were divided into groups based on amount smoked, the
data suggested that heavier smokers (≥15 cigarettes per day) were more likely to develop venous thromboembolism than lighter smokers (RRs 1.47 [1.34–1.62] and 1.29 [1.17–1.42]; \( P_{\text{heterogeneity}}=0.03 \)). A total of 2054 of the 4630 women with venous thromboembolism were diagnosed with pulmonary embolism (with or without deep vein thrombosis), whereas the remaining 2576 cases were diagnosed with deep vein thrombosis alone; similar patterns of increased risk for current smokers were seen for each of these 2 subgroups (Table 2).

We also investigated the RR of being admitted to a hospital for surgery in relation to smoking status, as well as the effect of smoking status on the risk of venous thromboembolism in the first 12 weeks after an operation (Table 3). There was a significantly increased RR of surgery for both past and current smokers compared with never-smokers (RR 1.12 [95% CI 1.12–1.13] for both categories), with heavier smokers having a significantly greater increased RR than lighter smokers (RRs 1.15 [95% CI 1.14–1.16] and 1.10 [95% CI 1.09–1.11], respectively; \( P_{\text{heterogeneity}}<0.0001 \)). Among women who underwent surgery, those who were current smokers at recruitment were more likely to be diagnosed with venous thromboembolism in the first 12 weeks after

### Table 1. Baseline Characteristics and Follow-up of Women Included in the Analyses, by Smoking Status at Recruitment

<table>
<thead>
<tr>
<th>Characteristics and Follow-up</th>
<th>All Women (n=1162718)</th>
<th>Never (n=596860)</th>
<th>Past (n=327839)</th>
<th>Current &lt;15 (n=122214)</th>
<th>Current ≥15 (n=115805)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>56.1 (4.8)</td>
<td>56.3 (4.9)</td>
<td>56.2 (4.9)</td>
<td>55.6 (4.6)</td>
<td>54.9 (4.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>26.1 (4.6)</td>
<td>26.1 (4.6)</td>
<td>26.6 (4.8)</td>
<td>25.2 (4.3)</td>
<td>25.8 (4.7)</td>
</tr>
<tr>
<td>Alcohol consumption, units/wk, mean (SD)</td>
<td>4.2 (5.3)</td>
<td>3.5 (4.6)</td>
<td>5.2 (5.9)</td>
<td>4.2 (5.3)</td>
<td>4.9 (6.5)</td>
</tr>
<tr>
<td>Lowest socioeconomic tertile, %</td>
<td>32.8</td>
<td>27.2</td>
<td>32.4</td>
<td>44.2</td>
<td>51.1</td>
</tr>
<tr>
<td>Current user of hormone replacement therapy, %</td>
<td>34.0</td>
<td>31.4</td>
<td>36.7</td>
<td>35.3</td>
<td>38.3</td>
</tr>
<tr>
<td>Strenuous physical activity &gt;1 time per week, %</td>
<td>21.1</td>
<td>21.8</td>
<td>22.9</td>
<td>18.4</td>
<td>14.7</td>
</tr>
<tr>
<td>History of diabetes mellitus, %</td>
<td>2.6</td>
<td>2.4</td>
<td>3.0</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>23.9</td>
<td>24.8</td>
<td>25.3</td>
<td>19.5</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Follow-up: without surgery*

| No. of women                  | 1162718           | 596860          | 327839          | 122214                 | 115805               |
| Person-years of follow-up     | 7282214           | 3849413         | 1996867         | 750339                 | 685595               |
| No. of venous thromboembolism cases | 4630         | 2226            | 1296            | 531                    | 577                  |

Follow-up: after surgery

| No. of women with ≥1 hospital admission for surgery during follow-up | 636549           | 313466          | 187031           | 68320                  | 67732                |
| Person-years of follow-up during 12 weeks after first operation | 144438           | 71189           | 42477            | 15466                  | 15307                |
| No. of venous thromboembolism cases during 12 weeks after first operation | 1852            | 893             | 549             | 198                    | 212                  |

*Includes person-years at risk and incident cases for women who did not have surgery during the entire follow-up period and person-years and incident cases before the first operation for women who had surgery.

### Table 2. In the Absence of Surgery, Adjusted Relative Risks by Smoking Status of Hospital Admission With or Death of Venous Thromboembolism (and Separately for Pulmonary Embolism and for Venous Thrombosis Without Pulmonary Embolism)

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Venous Thromboembolism*</th>
<th>Venous Thrombosis With Pulmonary Embolism†</th>
<th>Venous Thrombosis Without Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases (n=4630)</td>
<td>Adjusted RR (95% CI)</td>
<td>No. of Cases (n=2054)</td>
</tr>
<tr>
<td>Never</td>
<td>2226</td>
<td>1.00 (95% CI)</td>
<td>977</td>
</tr>
<tr>
<td>Past</td>
<td>1296</td>
<td>1.08 (1.01–1.16)</td>
<td>576</td>
</tr>
<tr>
<td>Current</td>
<td>1108</td>
<td>1.38 (1.28–1.48)</td>
<td>501</td>
</tr>
<tr>
<td>Current &lt;15 cigarettes/d</td>
<td>531</td>
<td>1.29 (1.17–1.42)</td>
<td>243</td>
</tr>
<tr>
<td>Current ≥15 cigarettes/d</td>
<td>577</td>
<td>1.47 (1.34–1.62)</td>
<td>258</td>
</tr>
</tbody>
</table>

*Population at risk=1162718 women. Relative risks are adjusted for region of recruitment, socioeconomic group, age, frequency of strenuous exercise, use of hormone replacement therapy, body mass index, alcohol consumption, history of hypertension, and history of diabetes.

†Diagnosis of deep vein thrombosis or pulmonary embolism.

CI indicates confidence interval; RR, relative risk.
surgery than never-smokers (RR 1.16 [95% CI 1.02–1.30]), with a suggestion of increasing risk with increasing amount smoked for current smokers, although this difference was not statistically significant (RRs 1.10 [95% CI 0.94–1.29] and 1.21 [95% CI 1.04–1.41] for <15 and ≥15 cigarettes per day, respectively; $P_{\text{heterogeneity}}$=0.4). The RRs of venous thromboembolism for current compared with never-smokers after day case and inpatient surgery separately were similar to the overall RR for current smokers after any type of surgery, although there were fewer cases and these risks were not statistically significantly increased (RRs 0.94 [95% CI 0.65–1.35] and 1.11 [95% CI 0.98–1.26] for day case and inpatient surgery, respectively).

Discussion

In this large prospective study of middle-aged women in the United Kingdom, we found that current smokers had an ≈40% greater risk of a hospital admission with, or death of, venous thromboembolism than never-smokers (adjusted RR 1.38 [95% CI 1.28–1.48]). Moreover, venous thromboembolism incidence was greater in heavier than lighter smokers. We also found that current smokers were more likely to be admitted to a hospital for surgery than never-smokers and were more likely to develop postoperative venous thromboembolism than never-smokers.

Findings in Relation to Previous Studies

The present finding that women who smoke are at an increased risk of venous thromboembolism is consistent with some6–10 but not all13,14 previous studies. A 2008 meta-analysis found no overall effect of smoking on venous thromboembolism risk in men and women combined (odds ratio 1.15, 95% CI 0.92–1.44); however, there was significant heterogeneity by study, and the relationship by amount smoked was not examined.12 Subsequent reports from cohort studies involving women are mixed: The Iowa Women’s Health Study found an increased risk of venous thromboembolism in smokers only for those with cancer14, conversely, results from 3 other cohort studies were consistent with the present findings, although these investigations had limited power to detect an association.6–10 A recent report from a large population-based case-control study also noted a relationship between smoking and venous thromboembolism in women: The odds ratio for current versus never-smokers was 1.55 (95% CI 1.33–1.82).7

The present study is the first to explore the relationship between smoking and the risk of postoperative venous thromboembolism in women. Moreover, the few investigations that have examined the independent effects of smoking on venous thromboembolism after surgery involved far fewer patients than the present study, and smoking was not the key exposure of interest.18–22 In those studies, no association was observed after elective hip replacement,18 hip or knee arthroplasty,19 colorectal surgery,20,21 or outpatient surgery.22

The present observation that current and past smokers were more likely to undergo surgery during follow-up than never-smokers was not unexpected given that smoking increases the risk of conditions such as cancer and cardiovascular disease5 that are frequently treated surgically. However, to the best of our knowledge, the relationship has not been explored directly previously.

The biological mechanism by which smoking might increase the risk of venous thromboembolism has not been confirmed. It has been postulated that activation of monocytes, granulocytes, and endothelial inflammation is the likely mechanism.1

The relationship between smoking and venous thromboembolism is important. First, despite a general downward trend of smoking prevalence among women in many high-income countries, smoking is still relatively common.30–32 Second, it has been reported that smoking interacts with other inherited and acquired risk factors for venous thromboembolism, including thrombophilic mutations,3,31 oral contraceptive use,7 and pregnancy.34–38

Study Strengths and Limitations

The present study has several strengths, including the large number of participants and the linkage of questionnaire data
with hospital admission, cancer registration, and death and emigration records. The linked data permitted the exclusion of women with a history of venous thromboembolism, cancer, or recent surgery at recruitment; provided information on a broad range of potential confounders; and ensured virtually complete follow-up for both hospital admission and deaths. As discussed previously, high accuracy rates have been reported for the coding of diagnoses and operations in NHS admissions data, the linkage between NHS data sets, and the identification of Million Women Study participants within those data sets. In addition, an underlying cause of death was recorded for 99.9% of cohort members who died during follow-up. Only 6% of eligible women did not provide information about smoking at recruitment, and their exclusion from the study is unlikely to explain our findings.

There are several aspects of the present study that merit further consideration. The large majority of women with pulmonary embolism would have been admitted to a hospital, but some with venous thrombosis alone may not have been (currently available NHS databases do not permit reliable estimation of how frequent this is). Smoking-associated RRs are similar for women with and without pulmonary embolism, so our conclusions are unlikely to be altered by some women with venous thrombosis not having been admitted to a hospital. Smoking status was based on self-report at recruitment, which, if anything, would result in underestimation of the risk of venous thromboembolism in current smokers. Validation studies show that self-report of smoking is reliable but the prevalence of smoking in this cohort has decreased substantially over the study period, resulting in smoking-related risks to be underestimated.

As in our previous investigation, in the present analysis we were able to minimize the potential for confounding by major risk factors for venous thromboembolism: Women with a history of venous thromboembolism, cancer, or recent surgery at recruitment were excluded, age was accounted for, and we adjusted for body mass index, hormone replacement therapy, physical activity, hypertension, diabetes mellitus, alcohol consumption, socioeconomic group, and region of recruitment. In the absence of surgery analysis, follow-up was censored at any cancer diagnosis or surgery (which included procedures to treat fractures and other trauma), and oral contraceptive use and pregnancy were improbable exposures in our study of middle-aged women. We cannot, of course, exclude the possibility that there were unmeasured confounders.

Study participants were not tested for inherited prothrombotic mutations; however, there is no reason to suppose that smokers are more likely to have thrombophilic disorders than never-smokers; indeed, the observation that venous thromboembolism risk was only marginally increased in past smokers argues against confounding by thrombophilia status as an explanation for our findings of a higher risk of venous thromboembolism in current smokers.

We were able to adjust for physical activity at recruitment and censor follow-up at surgery, but we had no information about other periods of immobility during follow-up, nor did we have information about the use of postoperative anticoagulation; however, to explain the excess risk of postoperative venous thromboembolism in current smokers, never-smokers would need to have been preferentially treated with anticoagulants. This seems unlikely, especially because never-smokers had a similar mean body mass index to smokers and were more physically active and less likely to take hormone replacement therapy than smokers.

Our exploration of the relationship between smoking and venous thromboembolism was restricted to women. As with the investigations that provided results for women, cohort studies that included men have produced inconsistent findings.

**Implications**

Our finding of a higher risk of venous thromboembolism in current smokers reinforces the importance of tobacco control strategies and their vital role in the prevention of disease and premature mortality. Although the 40% increase in venous thromboembolism incidence in smokers found here is not as great as the smoking-related increases in arterial diseases, in 2009 about 20% of United Kingdom women aged 50 to 59 years were smokers. Hence, a considerable proportion of venous thromboembolic events in women could be attributed to smoking. The present results also highlight the benefits of smoking cessation, because the risk of venous thromboembolism in past smokers was only marginally higher than that of never-smokers. Current clinical guidelines do not specify smoking as an additional risk factor for postoperative venous thromboembolism. The present findings suggest that smoking might also be considered in the assessment of venous thromboembolism risk in patients undergoing surgery.

**Appendix**

**Million Women Study Collaborators**

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We thank all of the women who participated in the study, staff from participating NHS Breast Screening Centres, the study steering committee, and ISD Scotland, the Information Centre for Health and Social Care, and Northgate Solutions for the linkage of hospital records.

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Disclosures

Valerie Beral is the Principal Investigator of the Million Women Study (research grant ≥810 000). The remaining authors report no conflicts.

References

Clinical Perspective

Evidence about the effect of smoking on the incidence of venous thromboembolism, generally and in the postoperative period, is limited and inconsistent. We linked questionnaire data on smoking in a large United Kingdom cohort study (the Million Women Study) with hospital admission and death records to study venous thromboembolism incidence in relation to smoking, both in the absence of surgery and in the 12 weeks after surgery. During 6 years of follow-up, 4630 women were admitted to a hospital for or died of venous thromboembolism. In the absence of surgery, the risk of venous thromboembolism in current smokers was 40% higher than in never-smokers, with the risk increasing the more cigarettes women smoked. Similar relationships were found for women with a pulmonary embolism and for women with venous thrombosis alone. Smokers were more likely than never-smokers to have surgery. In the 12 weeks after surgery, current smokers had significantly higher risks of venous thromboembolism than never-smokers. In conclusion, smoking is another factor to consider in the assessment of venous thromboembolism risk in patients undergoing surgery.

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Smoking, Surgery, and Venous Thromboembolism Risk in Women: United Kingdom Cohort Study
Siân Sweetland, Lianne Parkin, Angela Balkwill, Jane Green, Gillian Reeves, Valerie Beral and for the Million Women Study Collaborators
for the Million Women Study Collaborators

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SUPPLEMENTAL MATERIAL

Sweetland et al.; Smoking, Surgery, Venous Thromboembolism

Appendix

ICD codes used to identify venous thromboembolism before study entry and during follow-up:
ICD-9: 415.1, 451, 452, 453, 997.2, 671.3, 671.4, 671.9, 673.2, 634.6, 635.6, 636.6, 637.6, 638.6, and 639.6.
ICD-10: I26, I80, I81, I82, I97.8, I97.9, O22.3, O22.9, O87.1, O87.9, O88.2, O08.7, O08.2.

OPCS-4 codes excluded from definition of surgery:
All U codes, X28-X39, X44, X48-X58, X60-X62, X66, X70-X97