

Short Communication

Reproductive History and Pancreatic Cancer Incidence and Mortality in a Cohort of Postmenopausal Women

Richard J. Stevens,^{1,2} Andrew W. Roddam,² Jane Green,² Kirstin Pirie,² Diana Bull,² Gillian K. Reeves,² and Valerie Beral² on behalf of the Million Women Study Collaborators

¹Department of Primary Health Care and ²Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom

Abstract

There is inconsistent evidence about the effect of reproductive history on women's risk of pancreatic cancer. In the Million Women Study, a prospective cohort of middle-aged women in the United Kingdom, we examined associations between reproductive history and pancreatic cancer incidence and mortality, controlling for age, socioeconomic status, geographic region, body mass index, smoking, and history of diabetes. During 7.1 million person-years of follow-up in 995,192

postmenopausal women, there were 1,182 incident pancreatic cancers. Pancreatic cancer incidence and mortality did not vary significantly with age at menarche, number of children, age at first birth, breast-feeding, type of menopause, age at menopause, or time since menopause. Any effect of reproductive history and pancreatic cancer risk in women is likely to be weak, if it exists at all. (Cancer Epidemiol Biomarkers Prev 2009;18(5):1457–60)

Introduction

Results from some (1–6), but not all studies (7–12), have suggested that the risk of pancreatic cancer in women may vary with reproductive factors such as age at menarche, parity, age at first birth, history of breast-feeding, and age at menopause. Whether there is an association of pancreatic cancer risk with some reproductive factors remains an open question, in particular, parity, later age at menopause, and surgical menopause (7, 11, 12).

The Million Women Study is a prospective cohort study of middle-aged women in the United Kingdom, recruited between 1996 and 2001. We have reported elsewhere on the increased risk of pancreatic cancer in women who have diabetes, who smoke, or have greater body mass index (13). In this report, we present results on the relationship between female reproductive factors and pancreatic cancer incidence and mortality.

Materials and Methods

The Million Women Study has been described in detail previously (14, 15). Between 1996 and 2001, 1.3 million middle-aged women invited for routine breast screening in the U.K. National Health Service completed a study questionnaire and gave informed consent for inclusion in the study, including follow-up for cancer incidence and mortality from any cause through the National Health Service Central Registers. The Oxford and Anglia

Multi-Centre Research Ethics Committee approved the study.

The recruitment questionnaire included questions on age at menarche, the number of children, age at first birth (if any), current menopausal status, age at menopause, and medical history including history of bilateral oophorectomy.³ A question on length of breast-feeding in months for each birth was added to the baseline questionnaire after the first 9% were recruited.

We restricted this analysis to 995,192 postmenopausal women with no previous cancer (except nonmelanoma skin cancer) ages between 50 and 64 at the time of recruitment. Women whose menopausal status at recruitment was masked by hysterectomy or by use of hormone replacement therapy before natural menopause were considered postmenopausal only if they were aged 53 or greater at recruitment, as described previously (15). For analyses of type of menopause, age at menopause, and time since menopause, we included only women whose menopausal type could clearly be defined as either natural menopause (592,306 women) or menopause attributed to bilateral oophorectomy (77,696 women), and with a known age at menopause or bilateral oophorectomy. Eligible women contributed person-years to analyses of incident cancer from the date of recruitment to the study until the date of diagnosis with pancreatic cancer, date of death, or last date of follow-up, or date of loss to follow-up (e.g., through emigration), whichever was the earliest. Women registered with a cancer other than pancreatic cancer were censored at the date of diagnosis of that cancer. Cox proportional hazards models were applied using the

Received 11/28/08; revised 1/22/09; accepted 2/26/09.

Requests for reprints: Richard J. Stevens, Department of Primary Health Care, Rosemary Rue Building, Old Road, Oxford, OX3 7LF United Kingdom. Phone: 44-1865-289355; Fax: 44-1865-289287. E-mail: richard.stevens2@dphpc.ox.ac.uk

Copyright © 2009 American Association for Cancer Research.

doi:10.1158/1055-9965.EPI-08-1134

³ Questionnaire available at <http://www.millionwomenstudy.org/>.

Table 1. Characteristics at recruitment of postmenopausal women included in this analysis

	Population at risk	Incident cases of pancreatic cancer	Deaths from pancreatic cancer
N	995,192	1,182	1,516
Mean years of follow-up	7.1 for incidence; 8.9 for mortality		
Age in years, mean (SD)	57.3 (4.1)	58.7 (3.9)	58.7 (3.9)
Current smoker	21% (194,617)	33% (363)	34% (482)
Body mass index in kg/m ² , mean (SD)	26.3 (4.7)	26.6 (4.9)	26.4 (4.8)
History of diabetes	3.0% (29,387)	5.2% (61)	4.6% (70)
Socioeconomic status: upper third	33% (328,516)	32% (379)	31% (470)
Age at menarche, mean (SD)	13.0 (1.6)	13.0 (1.6)	13.1 (1.7)
Parous	89% (885,015)	87% (1,029)	88% (1,339)
No. of children, among parous women, mean (SD)	2.4 (1.1)	2.5 (1.2)	2.5 (1.2)
Ever breast-fed, among parous women	69% (477,477)	71% (533)	70% (685)
Age at menopause, mean (SD)*	49.2 (3.7)	49.3 (3.8)	49.4 (3.8)

*In 670,002 women with natural menopause or bilateral oophorectomy.

Stata computing package, taking attained age as the underlying time variable, stratifying by geographic region (10 regions) and socioeconomic status (quintiles of deprivation index; ref. 16), and adjusting for smoking (never, past, and current), body mass index (in six categories with cutpoints at 22.5, 25.0, 27.5, 30.0, and 32.5 kg/m²), and history of diabetes (yes or no), assigning missing values to a separate category where necessary. Time since menopause (in four categories with cutpoints at 10, 15, and 20 years) was analyzed as a time-dependent variable (17). Because there was no natural reference category for many variables (e.g., age at menopause), variances are, where appropriate, estimated by treating the relative risks as floating absolute risks. Results for categorical variables are therefore presented in a plot of relative risks and their corresponding floating SEs and 95% floating confidence intervals (18). Results for dichotomous comparisons (all parous versus nulliparous women, and bilateral oophorectomy versus natural menopause) are presented in the text as relative risks with conventional 95% confidence intervals. Proportional hazards assumptions were checked graphically.

Results

Table 1 shows the self-reported characteristics, at entry to the study, of the 995,192 postmenopausal women in this analysis. The cohort was followed for a mean of 7.1 years for incident cancer (total, 7.1 million person-years), during which time there were 1,182 incident cases of pancreatic cancer. The cohort was followed for a mean of 8.9 years for mortality (total, 8.8 million person-years), during which time there were 1,516 deaths from pancreatic cancer.

Figure 1 shows the incidence of pancreatic cancer by reproductive factors. Pancreatic cancer incidence did not vary significantly between categories of age at menarche, age at first birth, history of breast-feeding, age at menopause, or time since menopause. Compared with nulliparous women, all parous women combined were at lower risk of incident pancreatic cancer ($P = 0.01$), but within parous women, there was no trend with increasing number of children ($P = 0.8$). Women with bilateral oophorectomy were at a similar risk of pancreatic cancer to women with natural menopause (relative risk, 0.96;

95% confidence interval, 0.75-1.23; $P = 0.8$). When we repeated analyses testing for associations with pancreatic cancer mortality instead of incident pancreatic cancer, results were similar, except that there was no significant difference in mortality between nulliparous women and all parous women combined ($P = 0.2$).

Discussion

Reproductive factors including age at menarche, parity, age at first birth, breast-feeding, type of menopause, age at menopause, and time since menopause were not associated with risk of pancreatic cancer in this cohort.

The relationship between parity and pancreatic cancer risk has been inconsistent in previous studies (7-12). There was no trend in risk with increasing number of children in all women or in parous women, either for incidence or mortality. When all parous women were grouped together, there was a slightly lower risk than in nulliparous women, for pancreatic cancer incidence and not mortality, and the finding for disease incidence may well be due to chance.

In this study, we did not see any difference in risk between women with natural menopause and women whose menopause was attributed to bilateral oophorectomy. Of two previous prospective studies that have examined pancreatic cancer risk in relation to type of menopause, one found an elevated risk of incident pancreatic cancer in women with hysterectomy or bilateral oophorectomy compared with women with natural menopause (11), but another found no such association with pancreatic cancer mortality (9).

Most previous studies have found no association between pancreatic cancer risk and age at menopause (7, 9, 10). One recent study reported that women with a later menopause were at lower risk of incident pancreatic cancer, especially in women with a surgical menopause (11). By contrast, another study reported that women with a later menopause were at higher risk (12). Our study adds to the evidence that there is little or no association between age at menopause and risk of pancreatic cancer.

Breast-feeding history has been considered by just two previous prospective studies of pancreatic cancer (7, 12). Neither found significant results for breast-feeding,

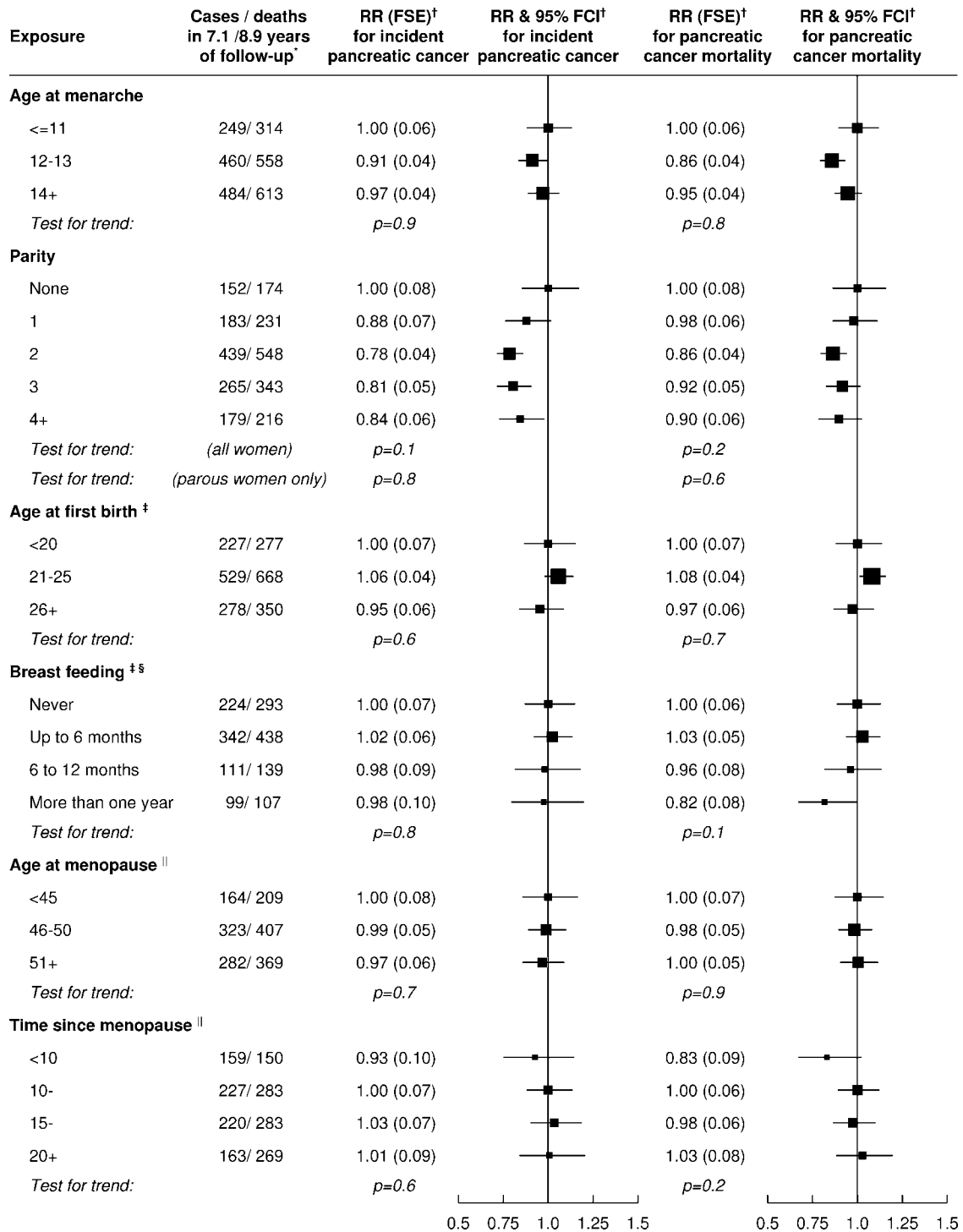


Figure 1. Relative risks of pancreatic cancer incidence by categories of age at menarche, parity, age at first birth, breast-feeding, type of menopause, age at menopause, and time since menopause. *, totals may not always agree due to a small number of missing values; †, RR, FSE, and FCI denote relative risk, floating SE, and floating confidence intervals controlling for age, region, socioeconomic status, smoking, body mass index, and diabetes as described in the text; ‡, in parous women only, adjusting additionally for level of parity; §, the question about breast-feeding was added to the questionnaire after the first 9% of women were recruited; ||, in women with natural menopause or bilateral oophorectomy.

Downloaded from <http://aacrjournals.org/cebp/article-pdf/18/5/1457/2269457/1457.pdf> by guest on 14 July 2024

although one found a possible interaction between parity and breast-feeding (12). With more cases of pancreatic cancer than both these studies combined, our results provide further evidence against an association between breast-feeding history and pancreatic cancer risk.

Early studies reported increased risk of pancreatic cancer in women with early menarche (1, 2). Our results are consistent with those from more recent studies in finding no association between pancreatic cancer risk and age at menarche (7-12). Previous studies have reported both positive (2) and inverse (19) associations between risk of pancreatic cancer and earlier age at first birth, but most studies find no such association, as do we (7-12).

To our knowledge, the results presented here include more women with incident pancreatic cancer (as opposed to pancreatic cancer mortality) than any previous prospective study. As in most large epidemiologic studies, reproductive history was self-reported. However, the prospective design of the study means that information on reproductive factors was recorded before follow-up began and should not be influenced by a subsequent diagnosis of cancer.

In conclusion, in this large prospective study, we found no strong evidence of any associations between reproductive history and pancreatic cancer incidence or mortality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

We are grateful to the women participating in the study and to the staff of the participating breast screening centres and coordinating centre. The Million Women Study is supported by Cancer Research U.K., the Medical Research Council, and the U.K. National Health Service breast screening programme.

References

- Bueno De Mesquita HB, Maisonneuve P, Moerman CJ, Walker AM. Anthropometric and reproductive variables and exocrine carcinoma of the pancreas: a population-based case-control study in the Netherlands. *Int J Cancer* 1992;52:24-9.
- Fernandez E, La Vecchia C, D'Avanzo B, Negri E. Menstrual and reproductive factors and pancreatic cancer risk in women. *Int J Cancer* 1995;62:11-4.
- Ji BT, Hatch MC, Chow W-H, et al. Anthropometric and reproductive factors and the risk of pancreatic cancer: a case-control study in Shanghai, China. *Int J Cancer* 1996;66:432-7.
- Karlsom BM, Wu J, Hsieh CC, Lambe M, Ekblom A. Parity and the risk of pancreatic cancer: a nested case-control study. *Int J Cancer* 1998;77:224-7.
- Duell EJ, Holly EA. Reproductive and menstrual risk factors for pancreatic cancer: a population-based study of San Francisco Bay Area women. *Am J Epidemiol* 2005;161:741-7.
- Lo AC, Soliman AS, El-Ghawalby N, et al. Lifestyle, occupational, and reproductive factors in relation to pancreatic cancer risk. *Pancreas* 2007;35:120-9.
- Skinner HG, Michaud DS, Colditz GA, et al. Parity, reproductive factors, and the risk of pancreatic cancer in women. *Cancer Epidemiol Biomarkers Prev* 2003;12:433-8.
- Navarro Silvera SA, Miller AB, Rohan TE. Hormonal and reproductive factors and pancreatic cancer risk: a prospective cohort study. *Pancreas* 2005;30:369-74.
- Teras LR, Patel AV, Rodriguez C, Thun MJ, Calle EE. Parity, other reproductive factors, and risk of pancreatic cancer mortality in a large cohort of U.S. women (United States). *Cancer Causes Control* 2005;16:1035-40.
- Lin Y, Kikuchi S, Tamakoshi A, et al. Association of menstrual and reproductive factors with pancreatic cancer risk in women: findings of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk. *J Gastroenterol* 2006;41:878-83.
- Prizment AE, Anderson KE, Hong CP, Folsom AR. Pancreatic cancer incidence in relation to female reproductive factors: Iowa Women's Health Study. *JOP* 2007;8:16-27.
- Heuch I, Jacobsen BK, Albrektsen G, Kvaele G. Reproductive factors and pancreatic cancer risk: a Norwegian cohort study. *Br J Cancer* 2008;98:189-93.
- Stevens RJ, Roddam AW, Spencer EA et al. Factors associated with incident and fatal pancreatic cancer in a cohort of middle-aged women. *Int J Cancer* 2009;142:2400-5.
- Million Women Study Collaborative Group. The Million Women Study: design and characteristics of the study population. *Breast Cancer Res* 1999;1:73-80.
- Million Women Study Collaborative Group. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362:419-27.
- Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the North. London: Croom Helm; 1988.
- Collett D. Modelling survival data in medical research. Texts in statistical science. USA: Chapman & Hall/CRC Press; 2003.
- Easton DF, Peto J, Babiker AGAG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991;10:1025-35.
- Kreiger N, Lacroix J, Sloan M. Hormonal factors and pancreatic cancer in women. *Ann Epidemiol* 2001;11:563-7.