Screening and the association between cervical cancer and known reproductive and hormonal factors



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This thesis is dedicated to the memory of my parents and my niece and friend, Kui who saw this work started but did not live to see it finished.

Acknowledgements

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Abstract

Epidemiological studies have shown associations between reproductive and hormonal factors and cervical carcinogenesis, but have had limited information on previous cervical screening. Screening is known to reduce the incidence of invasive cervical cancer (ICC) and there is some evidence that reproductive and hormonal factors affect screening uptake. The main aim of this thesis was to examine the risk of cervical neoplasia i.e., pre-invasive cervical intraepithelial neoplasia grade 3 (CIN3) and ICC, associated with reproductive factors, namely parity and age at first birth, and hormonal factors, namely use of oral contraceptives (OC) and menopausal hormone therapy (MHT), taking into account confounding by screening history.

Analyses involved over 800,000 women in the Million Women Study with linked NHS Cervical Screening Programme records, including over 1400 cases of CIN3 and 1000 cases of ICC. Using logistic regression, non-attendance for cervical screening was found to vary considerably according to reproductive and hormonal factors. Using Cox regression to estimate relative risks of cervical neoplasia, I found that early childbearing was associated with increased risks of CIN3 and ICC after adjustment for multiparity. For hormonal factors, while use of OCs was not associated with overall ICC, there were heterogenous associations by histo-type. In particular, among users of OCs risks were increased for squamous cell carcinoma (SCC) but reduced for adenocarcinoma (AC). The increased risk of SCC with increasing duration of use of OCs persisted for up to 30 years after cessation of use. Use of MHT was associated with a reduction in risk of ICC which was also heterogenous by histo-type; for SCC there was a significant reduction in risk with MHT use, but no significant association with AC.

This large prospective analysis confirms that early childbearing contributes to cervical neoplasia risk and suggests that long duration use of OCs confers a persistent risk of invasive SCC. This study also provides new evidence that hormonal risk factors for cervical cancer may vary between the two major histo-types, SCC and AC, highlighting the need for further research on these cancers.

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List of Abbreviations

ICC . . . . . Invasive cervical cancer

CIN3 . . . . . Cervical intraepithelial neoplasia, grade 3 (CIN3)

CIS . . . . . Carcinoma *in situ*

SCC . . . . . Invasive squamous cell carcinoma of the cervix

AC . . . . . Invasive adenocarcinoma of the cervix

HPV . . . . . Human Papilloma Virus

HrHPV . . . . High-risk Human Papilloma Virus

FTP . . . . . Full-term pregnancy

OC . . . . . Oral contraceptive

MHT . . . . . Menopausal hormone therapy

AFSI . . . . . Age at first sexual intercourse

MWS . . . . . Million Women Study

NHSCSP . . . NHS Cervical Screening Programme

IARC . . . . . International Agency for Research on Cancer

Write that which should not be forgotten

— Isabel Aliende

1 Thesis introduction

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1.1 Rationale

Worldwide, invasive cervical cancer (ICC) is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 604,000 new cases and 342,000 deaths in 2020.[1] The vast majority of cervical cancers are epithelial tumours (carcinomas) and of these, the majority of cases are squamous cell carcinoma [SCC] (75-90%). The next most common type is adenocarcinoma (AC), the proportion of which varies between 5% and 26% worldwide.[2]

Nearly all cases of ICC are caused by persistent infection with high-risk types of the Human Papilloma Virus (HPV).[3] Current perspectives of the stages in cervical carcinogenesis include HPV infection; persistence rather than clearance of the virus; linked to the progression to high-grade precursor lesions such as cervical intraepithelial neoplasia, grade 3 (CIN3); and finally invasion to cancer.[4] However, HPV infection alone may not be sufficient to cause ICC and other factors, known as co-factors, have been found to influence the risk of ICC and its immediate precursors in conjunction with HPV.[5]

Various reproductive and hormonal factors, including long-term hormonal contraceptive use, younger age at first full-term pregnancy (FTP) and multi-parity, have been suggested to be etiologic co-factors associated with an increased risk of cervical neoplasia, i.e., CIN3 and ICC including separately by major histo-type, SCC and AC.[6–8] The predominant hypothesis for these associations is exposure to oestrogens and progesterone which are thought to interact with hormone receptors present in cervical tissue and promote HPV persistence or progression.[5, 9, 10] It is therefore possible that other exogenous hormones, such as menopausal hormones, could also have a role in cervical carcinogenesis and indeed limited data implies that the use of menopausal hormone therapy may reduce the risk of ICC.[11–13]

Cervical cancer is largely preventable by cervical screening, which deliberately interrupts the natural history of cervical cancer by the detection and treatment of precursor lesions preventing the development of ICC. For this reason, a history of attendance for cervical screening is widely accepted to be associated with an

increase in the incidence of pre-invasive or *in-situ* cancers in the short-term,[14, 15] and in the long-term, has been established as causally associated with a reduction in the incidence of ICC based on the aggregate of numerous time-trend analyses and observational studies.[16] However, for screening programmes to be effective in reducing the incidence of invasive cervical cancers, they must maintain high attendance.[17] Attendance rates vary widely across countries and settings, [18] and there is evidence that certain personal factors, including reproductive and hormonal factors, are associated with non-attendance for screening.

Given the associations between screening and the incidence of cervical neoplasia, as well as screening and reproductive and hormonal factors, there is scope to expand epidemiological analyses between reproductive and hormonal factors and the risk of cervical neoplasia taking into account the potential confounding effect of screening history. Although several individual studies and large collaborative analyses have attempted this,[6–8] their findings have been limited by a lack of detailed information on screening history, primarily retrospective design (with consequent risk of bias) or insufficient numbers of cases of the less-common adenocarcinoma to explore associations separately between histo-types.

1.2 Aims of Thesis

The overall aim of this thesis is to investigate the risk of cervical neoplasia i.e., CIN3 and ICC, associated with reproductive and hormonal risk factors adjusting for a woman's previous screening history in a unique dataset comprising a large UK prospective cohort study with linked NHS Cervical Screening Programme (NHSCSP) records. Specifically this thesis will:

1. Define a woman's screening history, in terms of previous attendance and previous test results at previous screening.

2. Examine the association between personal factors, including reproductive and hormonal factors, and cervical screening non-attendance.

3. Examine the association between screening history as defined and the risk of cervical neoplasia.

4. Examine the associations between age at first full-term pregnancy and parity including number of full-term pregnancies and the risk of cervical neoplasia adjusting for screening history as defined.

5. Examine the associations between oral contraceptives and menopausal hormone therapy use and the risk of cervical neoplasia adjusting for screening history as defined.

1.3 Thesis Outline

- **Chapter 1** provides an overview of the thesis, outlining the rationale—namely that although several studies have reported on the associations of reproductive and hormonal factors with cervical cancer risk, questions remain about whether, or to what extent, risk is affected by a woman's cervical screening history. This chapter also presents the aims of the thesis and the statement of contribution to work.

- **Chapter 2** provides a summary on cervical cancer, including natural history, risk factors and trends in epidemiology. This chapter also presents an introduction to cervical cancer screening and its effect on cervical cancer in relation to the natural history and trends in epidemiology.

- **Chapter 3** introduces a large prospective cohort of UK women, the Million Women Study (MWS), which is the main data source used for analyses in this thesis. It also introduces the NHS Cervical Screening Programme records, and describes the linkage of the MWS and NHSCSP. This chapter also describes assessment of exposure variables as well as cervical tumour variables, and summarises the main methods used for the epidemiological analyses subsequently presented in this thesis (Chapters 5-8)

- **Chapter 4** reports on the associations between a wide-range of personal factors including socio-demographic, behavioural, reproductive and hormonal factors and non-attendance for cervical screening within the MWS and NHSCSP dataset. It also reports on associations with personal factors within attenders classified as poor and good attenders.

- **Chapter 5** investigates the association between screening history, in terms of screening attendance and previous screening test results, and the risk of pre-invasive cervical cancer (CIN3) and ICC including separately by major histological tumour type, SCC and AC. This study is a prospective analysis in the MWS cohort, of 1,479 cases of CIN3 and 1,025 cases of ICC that had accrued by 31st December 2018. See **Chapter 3 Section 3.6.1** for details on case numbers for Chapters 5-8.

- **Chapter 6** investigates the association between reproductive factors (age at first FTP and parity including number of FTPs) and the risk of CIN3, ICC, SCC and AC. This study is a prospective analysis in the MWS cohort with 1,468 and 1,022 cases of CIN3 and ICC respectively that had accrued by 31 December 2018

- **Chapter 7** investigates the association between oral contraceptives and the risk of CIN3, ICC, SCC and AC. This study is a prospective analysis in the MWS cohort, of 1,465 cases of CIN3 and 1,016 cases of ICC, that had accrued by 31st December 2018.

- **Chapter 8** investigates the association between menopausal hormone therapy and the risk of CIN3, ICC, SCC and AC. This study is a prospective analysis in the Million Women Study cohort, of 1,255 CIN3 and 947 ICC cases that had accrued by 31st December 2018, amongst postmenopausal women.

- **Chapter 9** summarises the findings of this thesis, discusses the overall strengths and limitations, and provides suggestions for future work.

1.4 Role of the author in the preparation of this thesis

The research presented in this thesis is my own, conducted under the supervision of Professor Dame Valerie Beral, Dr. Isobel Barnes and Dr Siân Sweetland. The initial concept of investigating the effect of adjusting for screening history on the association between reproductive and hormonal factors and cervical cancer in the Million Women Study was originally developed during discussions with my supervisors. With guidance from my supervisors, I conducted all statistical analyses, produced all relevant tables and figures and drafted the text. To produce some of the figures, I used the R package 'Jasper' developed by Matthew Arnold.

I have also benefited from contributions from colleagues at the Cancer Epidemiology Unit (CEU) as follows: 1) Linkage to the NHSCSP screening data was performed by Dr. Roger Blanks and Rupert Alison with details provided in **Chapter 3, Section 3.2.3.2**; 2) The technique used for conducting tests for heterogeneity by histotype in **Chapters 5-8**, using a competing risks approach[19] was adapted from STATA code originally written by Kirstin Pirie (a senior statistical programmer at CEU); 3) My approach to the analyses on the risk of cervical neoplasia associated with MHT use was influenced by previous work in the Million Women Study by study investigators led by Professor Gillian Reeves (head of the CEU); and 4) The idea to initiate a study in Kenya using data from the cancer registries in Nairobi and Eldoret was my own, but I have benefited from input and discussion with Dr. Yvonne-Joko Walburga (a former DPhil student at CEU) and Dr. Ann Korir (Head of the Nairobi Cancer Registry, Kenya Medical Research Institute).

Anything can be a good starting point for curiosity when you have yet to get to the stage of supposedly knowing where your interests lie

— Alain de Botton

2

Overview of cervical cancer

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2.1 Introduction

The cervix is the lower part of the uterus projecting into the vagina. It is made up of an endocervical canal (endocervix) leading into the uterus and an external opening to the vagina known as the ectocervix.[20] Two histologically distinct epithelia line the two regions of the cervix: squamous epithelium covers the outer ectocervix extending into the vagina, while glandular cells, also known as the columnar epithelium, line the inner endocervix. (see **Figure 2.1**) The cervical transformation zone is an area of metaplastic tissue between the squamous and glandular tissue and is especially susceptible to carcinogenesis, with nearly all invasive cervical cancer originating from this ring of epithelium.[4, 21] Two primary histological subtypes account for the vast majority of these tumours, corresponding to the two epithelia linings; squamous cell carcinoma which accounts for 75-90% of cases and glandular carcinoma (adenocarcinoma) whose proportion varies between 5% and 26% worldwide.[2]

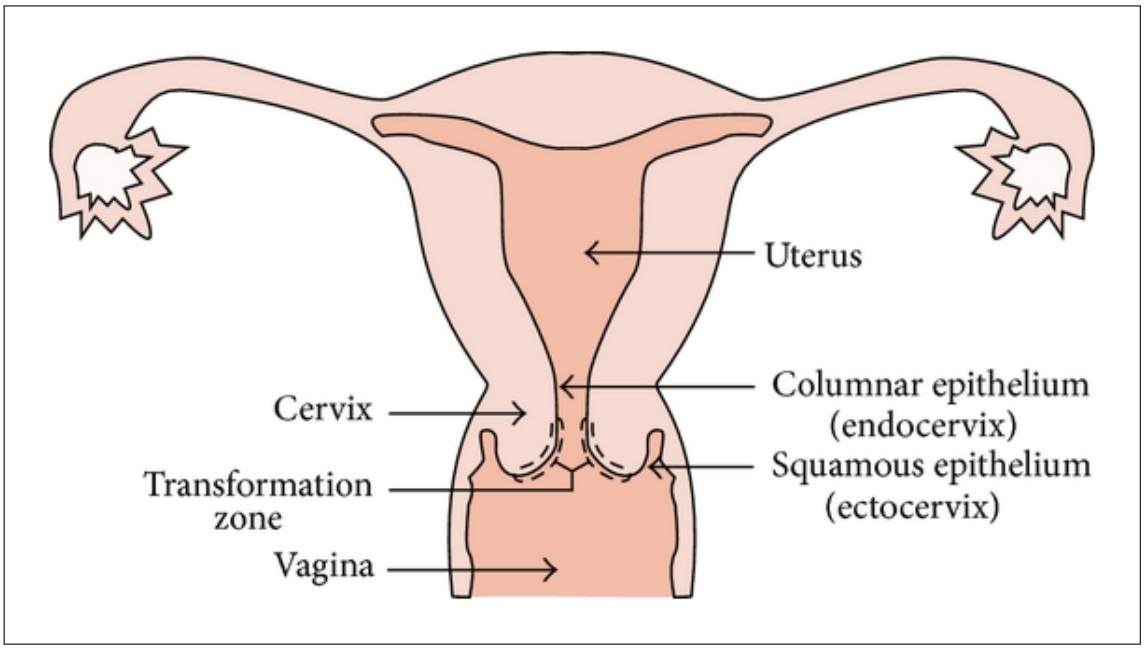

Figure 2.1: Anatomy of the uterine cervix and the transformation zone [22]

2.2 Natural History

Epidemiological evidence has long suggested that cervical cancer had to be the result of a sexually transmitted infection.[23] In the early 1980s, the central causal role of persistent Human Papilloma Virus (HPV) infection in the development of the majority of cervical squamous cell carcinomas (SCC) and adenocarcinomas (AC) was first demonstrated and is now well established.[3, 24] The stages in HPV-induced cervical carcinogenesis are now understood to include: HPV infection; persistence, rather than clearance of the virus; progression to precursor lesions; and invasion.[4] The natural history of AC is less well understood [25, 26] and it is unclear whether the stages of progression are similar to those widely accepted for SCC which are presented in **Figure 2.2**. What follows is a brief introduction to each stage of the natural history pathway as it relates to SCC. Current perspectives on the natural history of AC are then presented in **Section 2.2.2**

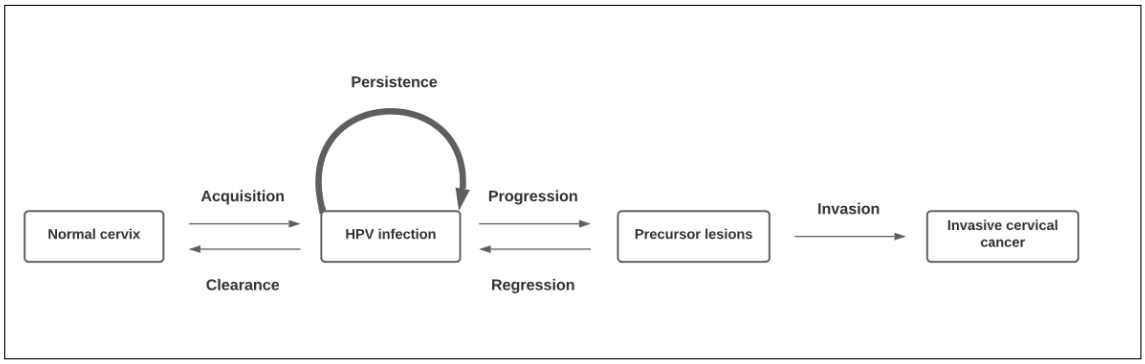

Figure 2.2: Cervical cancer natural history model

2.2.1 Squamous cell carcinoma

2.2.1.1 HPV Infection

HPV is a common sexually transmitted infection and most women will be infected over their lifetime.[27] The age-specific prevalence curve of cervical HPV infection as measured by HPV DNA confirms sexual transmission, with a large peak following typical population norms of sexual initiation in early adulthood.[28] The risk of acute HPV infection is generally associated with sexual behavioural factors that increase

the chances of an encounter with an infected person. Several observational studies of HPV prevalence and incidence have found that the most consistent predictor of infection is sexual behaviour, particularly number of sexual partners[29–32] and most notably recent sexual partners.[33–36] Early age at first sexual intercourse (AFSI) has also been found to be associated with an increased risk of HPV infection in some older studies,[28, 37–39] but not in more recent investigations.[29]

Fortunately while frequent, new HPV infections are mostly transient and have very high spontaneous clearance; half of the infections clear within 6 months, two thirds within 12 months, and around 80% within 2 years.[40] Persistence of HPV infection, i.e., long-duration detectable infection, is considered a prerequisite for cancer[4]. In other words, the longer the infection lasts the higher the likelihood that it will persist and progress to precursor lesions and potentially invasive cancer.[40, 41]

The carcinogenic activity of HPV is linked to the activity of two oncoproteins, E6 and E7 which integrate into the genome and inactivate tumour suppressor proteins p53 and retinoblastoma (Rb) interfering with cellular pathways that lead to apoptosis (programmed cell death). A series of pathological events is consequently triggered including irregular proliferation, elimination of cell cycle checkpoints and chromosomal instability leading to the development of cancer cells i.e., cells which grow forever unlike normal cells.[9, 24, 42]

2.2.1.2 Progression to cervical precursor lesions and invasion

The critical step in ICC carcinogenesis for most women is whether precursor lesions develop as an (uncommon) outcome of infection. Precursor lesions are characterised by first cytological (cellular) and eventually histological (tissue) abnormalities, which may progress to invasive cancer or regress i.e. decrease in severity. Historically, many screening programmes have detected cellular abnormalities via cytological smear testing commonly known as "Pap smears", although this practice is currently changing in favour of primary testing for HPV at screening. When cellular abnormalities are detected at screening women may be referred for colposcopy, a diagnostic procedure involving the use of a lighted microscope to closely examine

the cervix, during which histological abnormalities may be diagnosed. Histologic diagnoses, discussed in the following section, define the underlying neoplastic process and guide treatment, while cytological diagnoses serve to point towards probable underlying histology. (see **Figure 2.5**) Cytological smears are discussed in relation to cervical screening in **Section 2.4.3.1**.

A note on terminology

The terminology for squamous precursor lesions has evolved over time as understanding of underlying biology has changed and is summarised and compared in **Table 2.1**. Traditionally, precursor abnormalities capable of progression were categorised in a two-tier system: dysplasia (mild, moderate or severe) and carcinoma *in situ* (CIS).[43] However, to reflect the understanding of precursor lesions as a biological continuum versus two distinct entities, the concept of cervical intraepithelial neoplasia (CIN) was proposed in the 1960s: CIN1 replaced mild dysplasia, CIN2 replaced moderate dysplasia and CIN3 encompassed severe dysplasia and CIS.[44] Most recently, although yet to be widely adopted, the Lower Anogenital Squamous Terminology (LAST) conference in 2012 proposed a new two-tier system for HPV progression based on staining for p16, a biomarker of disruption by HPV of the Rb pathway which regulates cell cycle progression and cell death. In this case, low grade squamous intraepithelial lesion (LSIL) reflects all CIN1 and p16-negative CIN2; and high-grade squamous intraepithelial neoplasia (HSIL), represents a cancer precursor to be treated i.e., CIN2 (positive for p16) and CIN3.[45]

In the U.K, the three-tier cervical intraepithelial neoplasia (CIN) terminology is still used for the histological reporting of squamous precursor lesions[46] and is used in the rest of this thesis.

Table 2.1: Comparison of cervical squamous histology terminology categories

Natural history model	Dysplasia terminology	CIN terminology	LAST terminology
Infection	Negative	Negative	
	Mild dysplasia	CIN1	LSIL*
Precursor lesions	Moderate dysplasia	CIN2	HSIL*
	Severe dysplasia	CIN3	
	Carcinoma *in situ*		
Cancer	Carcinoma	Carcinoma	Carcinoma

Abbreviations: CIN, cervical intraepithelial neoplasia; LAST, Lower Anogenital Squamous Terminology; LSIL, low-grade squamous intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial neoplasia
*LAST terminology: p16-negative CIN2 is combined with CIN1 to form LSIL; and p16- positive CIN2 is combined with CIN3 to form HSIL

Cervical intraepithelial neoplasia

CIN is the graded spectrum of precursor squamous histological abnormalities. CIN grades 1-3 correspond to the degree of extension of abnormality within the cervical epithelium in thirds, with CIN grade 3 (CIN3) representing the involvement of more than two-thirds of the entire epithelium.[47] However, the grading tends to be subject to high rates of inter- and intraobserver variability, more so for CIN1 than for CIN3.[48]

CIN grades 1-3 are generally thought to have increasing risk of developing into invasive cancer and decreasing likelihoods of regression.[49] Current research suggests, however, that CIN1 may largely represent a histologic diagnosis of acute HPV infection which regresses spontaneously within 1-2 years and is unlikely to be a true cervical cancer precursor lesion.[48] Similarly, there is growing evidence to suggest that CIN2 may have little actual invasive potential forming a borderline category between acute transient infection and the more likely cancer precursor, CIN3.[50, 51] Natural history study investigations have reported that only 1% of CIN1 and 5% of CIN2 would progress to invasive cancer if left untreated.[49] CIN3 therefore represents the most established and most severe precursor lesion in the natural history of ICC i.e. most likely to progress. For the most part, CIN3 progression rates are largely derived from predictive modelling studies and rates of between 12% and 40% have been reported.[52–54] The most direct estimates for the progression rate of CIN3 derive from an unethical study of women with biopsy verified CIN3/CIS for which treatment was withheld or delayed in New Zealand in the late 1960s. Compared to progression rates of 0.7% in women who received adequate treatment during the 30 year follow-up period, progression rates were about 30% for all women who were not treated and about half of the women who had persistent CIN3 after 2 years developed ICC.[55]

2.2.2 Adenocarcinoma

As previously mentioned, cervical ACs are less common than SCCs, and their natural history is less clear.[56] Whereas the stages of progression may be similar to those of SCC i.e., starting with a HPV infection then progression to (glandular) cervical precursor lesions and finally invasive carcinoma, some evidence proposes that the natural history of AC may be different: either showing more aggressive (quicker) progression through the conventional stages presented in **Figure 2.2** or showing progression through fewer stages.[57]

Currently, putative stages in the natural history of HPV-related AC are atypical glandular cells (AGC), adenocarcinoma *in situ* (AIS) also known as cervical glandular intraepithelial neoplasia (CGIN), and finally invasive adenocarcinoma. CGIN is the most well-defined precursor lesion for AC although studies on its potential for progression are lacking.[2] Earlier precursor glandular lesions (AGC) are more difficult to define than squamous lesions as they are more diverse, have been rare in biopsies,[2, 58] and it has been shown that glandular precursor lesions tend to co-exist with squamous precursor lesions in over two-thirds of diagnoses.[59, 60]. Further, there is now increasing evidence that adenocarcinomas may represent a more heterogeneous group of tumours than SCC, and whilst most AC is HPV-related a good portion of ACs (10-15%) may not be and the natural history of these non-HPV related AC is even less clear.[61]

2.3 Aetiology

HPV infection alone may not be sufficient to cause ICC, and other factors known as co-factors have been demonstrated to influence persistence and progression to ICC and its immediate precursor, CIN3.[5] Etiologic co-factors that have been identified include viral, genetic and personal factors

2.3.1 Viral factors

The most important viral factor is viral type. HPV comprises a family of viruses of over 200 types which are loosely classified as low-risk (LrHPV) and high-risk (HrHPV) types according to their carcinogenic potential.[62] Twelve HrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) have been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC).[63] Of these, the most important HrHPV type is HPV16, which has been shown to be responsible for about half of all cervical neoplasia diagnoses i.e CIN3 and ICC. [64–66]. The next most important type is HPV18 which has been shown to be preferentially responsible for AC.[67] Together HPV 16 and 18 are known to account for 70% of all CIN3 and ICC.[68] Direct information on HPV status was not available for analyses in this thesis, however, proxy measures are included and discussed.

2.3.2 Genetic factors

Genetic factors influencing the immune response to HPV exist but are poorly understood with few polymorphisms studied showing consistent associations.[69] Human leukocyte antigen (HLA) genes have been most consistently associated with HPV infection control; some HLA gene anomalies are associated with an increased risk of HPV infection progressing to cancer,[70, 71] while others with a protective effect.[72] Genetic susceptibility is beyond the scope of this thesis.

2.3.3 Personal factors

Most of what is currently known on personal characteristics as co-factors stems from a series of meta-analyses published by the International Collaboration of

Epidemiological Studies of Cervical Cancer ("the Collaboration") who pooled individual participant data from all epidemiological studies with information on cervical cancer and certain potential risk factors. The Collaboration has reported on associations between CIN3/CIS and ICC risk and the use of hormonal contraceptives,[6] reproductive factors (parity and age at first full term pregnancy (FTP)),[7] tobacco smoking[73] and sexual behaviour.[74]

The results of the Collaboration meta-analyses are summarised briefly below. Further detail along with subsequently published evidence is reviewed and discussed in respective reproductive and hormonal factors analysis chapters (**see Chapters 6- 8**).

2.3.3.1 Reproductive factors

In terms of parity, the risk of ICC significantly increased with increasing number of FTPs, after controlling for age at first FTP (RR 1.76, 95% CI: 1.53-2.02 for 7+ FTPs vs 1-2). For CIN3/CIS, no significant trend was found for increasing numbers of FTPs, after controlling for age at first FTP. Early age at first FTP was associated with an increased risk of both ICC and CIN3/CIS and risk trends for age at first FTP were largely unaffected by reciprocal allowance for number of FTPs. These findings were consistent with those obtained in analyses restricted to high-risk HPV (HrHPV) positive women.[7]

Oestrogen levels increase markedly during pregnancy/birth and oestrogen has been suggested to contribute to risk via stimulating HPV carcinogenesis.[5] (**See Section 2.2.1.1**) Early age at first FTP also increases lifetime exposure to HPV which could explain an increase in cervical cancer risk.[75]

2.3.3.2 Hormonal factors

Among current users of oral contraceptives (OC) for 5 or more years, the risk of ICC was about double that of never users (RR 1.90, 95% CI: 1.69-2.13). The excess risk associated with OC use was found to decrease after cessation and largely disappear after 10 or more years. A similar pattern of risk was also seen for CIN3/CIS: among current users of OCs, the risk of CIN3/CIS increased with increasing duration of use and declined with increasing time since last use. However, unlike the risk of

ICC, there was a persistently elevated risk of CIN3/CIS after 10 or more years since last use. A similar pattern of risk was seen both for invasive and *in-situ* cancer in women who tested positive for HrHPV.[6]

Much less is known about the association between menopausal hormone therapy (MHT) and ICC or CIN3. In a recent prospective analysis from the European Prospective Investigation into Cancer and Nutrition (EPIC) study in Europe, it was reported that ever use of MHT was associated with a reduction in risk of ICC compared to never use (RR: 0.5, 95% CI: 0.4–0.8).[11] This result was similar in a nested case-control study within the same study allowing for the adjustment for HPV serology. However, both cohort and case-control analyses were based on small numbers with limited adjustment for potential confounding. Overall, there is some suggestion of a protective association with the use of MHT, but evidence is extremely limited.[12, 13]

Again, a possible mechanism to explain the associations between OC and/or MHT use and ICC risk is that oestrogen may interact with hormone receptors present in cervical tissue, which may influence the natural history of HPV infections [5]

2.3.3.3 Sexual behaviour

Relative risks of ICC have been reported to increase with lifetime number of sexual partners (trend: $p< 0.001$) with an approximately 3-fold higher risk for women with ≥ 6 partners vs 1 partner in fully adjusted analyses (RR: 2.78, 95%: 2.22-3.47). Similarly, the risk of ICC was found to be doubled for women with an earlier age at first sexual intercourse [AFSI] (RR: 2.05, 95% CI: 1.54-2.73 for ≤ 14 vs. ≥ 25 years at first sexual intercourse). The association with CIN3/CIS for lifetime number of sexual partners was similar; however, the association with AFSI was weaker than for ICC.[74]

The exact mechanisms for sexual behaviour factors are uncertain, however they are hypothesised to relate to increased HPV infection exposure (with increased lifetime number of sexual partners[29]) or increased duration of HPV infection (with earlier AFSI).[75] The interpretation of findings with an adjustment for HPV is

also potentially complicated due to these hypothesised mechanisms.[73] Information on sexual behaviour was not available for this thesis, however proxy measures are discussed in respective chapters.

2.3.3.4 Tobacco smoking

The Collaboration found that the relative risk of ICC associated with current smoking was highly heterogeneous by histo-type, i.e. for SCC and AC (case-case comparison $p<0.001$), and results were presented separately. There was an approximately 50% higher risk of invasive SCC in current smokers compared to never smokers, however they were not at increased risk for AC (RR: 1.46, 95% CI: 1.32–1.61 and RR: 0.92, 95% CI: 0.75–1.12 for SCC and AC respectively). The risk for SCC was also found to increase with the number of cigarettes smoked per day and with decreasing age at starting smoking. Similar patterns were reported for CIN3/CIS and adenocarcinoma *in situ* (AIS). Results were similar in analyses restricted to HrHPV-positive cases and controls.[73]

It has been proposed that tobacco may impair the immune system and smokers, unable to mount an effective immune response, maintain cervical HPV infections longer and have a lower probability of clearing an carcinogenic infection than never smokers.[76] Analyses on smoking as a risk factor are beyond the scope of this thesis, however smoking status is included as an adjustment variable in all analyses.

Squamous cell and adenocarcinoma

Current views on how personal co-factors compare by histo-type are also derived from a meta-analysis conducted by the Collaboration, bringing together 12 epidemiological studies with individual data on 8,097 women with SCC and 1,374 women with AC. In this paper, there were no significant differences between SCC and AC with respect to majority of the personal factors considered: number of sexual partners, AFSI, age at first FTP, body mass index and use of OCs. However, there was strong evidence ($p<0.001$) that current smoking may have a stronger effect on SCC than AC as discussed in **Section 2.3.3.4** above. Similarly, there was some evidence that parity may also be a stronger risk factor for SCC than for AC with

the relative risks for both histo-types increasing with increase in number of FTPs (RR vs 1-2 FTPs was 2.08, 95% CI: 1.95-2.23 and 1.61, 95% CI: 1.37–1.90 for 5+FTPs for SCC and AC respectively compared to women without cervical cancer), and the case-case comparison showed a significantly greater trend for SCC vs. AC (p=0.01).[8] As mentioned (see **Section 2.2.2**) there is now some evidence to suggest that adenocarcinomas may be a heteregenous group of cervical cancers with disparate origins but there is little prospective evidence on the risk factors by histo-type. The Collaboration analyses,[6, 7, 73, 74] which are largely comprised of retrospective studies, form the largest study on risk factors by histo-type.

2.4 Screening

Screening i.e., a secondary prevention intervention for cervical cancer, is discussed in this section. However, it is worthwhile to note that in the U.K. primary prevention i.e. HPV vaccination was rolled out to young girls aged 12-13 in 2008 and extended to young boys of the same age in 2019.[77] Large RCTs have proven that the three HPV vaccines that have been approved for use in the UK are highly effective in preventing new infections with HPV16 and HPV18,[78] and recent observational evidence shows a substantial reduction in the incidence of CIN3 and ICC in young women after the introduction of HPV vaccination in England.[79] However, it will be several decades before most women will benefit from the vaccines, and until then, cervical screening will remain the primary preventive strategy.

2.4.1 Definition and principles

The Commission on Chronic Illness (CCI) Conference on Preventive Aspects of Chronic Disease, held in 1951,[80] defined screening as the "*presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population.*"— a definition maintained by the WHO to date.[81, 82] A screening test should allow as few as possible with the disease to get through undetected (high sensitivity) and as few as possible without the disease to be subject to further investigation (high specificity). Cervical screening for precursor lesions satisfies the Wilson and Jungner criteria for the appropriateness of a screening programme: cervical cancer is associated with high morbidity and mortality, the natural history is well known, it has an identifiable pre-clinical stage, and treatment of precursor lesions or early stage ICC leads to better outcomes.[81]

2.4.2 Screening and cervical cancer

Cervical cytological screening has only been recently been assessed in a randomised controlled trial (RCT) which are the most reliable way to evaluate changes in incidence following exposure to screening, although persuasive evidence comes from

numerous ecological (time-trend)[15, 83–92] and observational studies in countries with organised cervical screening programmes. The RCT and observational studies are reviewed more comprehensively in Chapter 5

Time trends from the Nordic countries have shown that both incidence of and mortality from cervical cancer declined following the implementation of cervical screening programmes in the mid 1960s.[87, 93] The decline was greatest in Finland, where age-standardised (according to world standard) incidence and mortality decreased by almost 80%, from 13 cases per 100,000 women in 1960 to below 2 per 100,000 for incidence and 6.1 to 1.4 cases per 100,000 for mortality by the start of the 1990s.[85, 86] (**See Figure 2.3**) Estimated declines in incidence and mortality through the 1990s were comparable in Iceland, Sweden and Denmark, with variation attributable to differences in coverage of the target population and screening implementation policy with respect to age-ranges, intervals and follow-up for abnormal screens.[87]

In the U.K., screening was introduced in a in a disorganised fashion in 1966 with inadequate policy on which women ought to be screened, little evidence on how often women should be screened, and inadequate follow-up for women with positive results.[94] The flaws of this approach led to the inception of the centrally organised, population-based NHS Cervical Screening Programme in 1988 which resulted in a rapid decrease in age-standardised (according to world standard) incidence rates, from 16 per 100,000 women in 1970 to 10 per 100,000 women in 1995.[15] With respect to mortality, by the end of the 1990s age-standardised mortality had fallen to 3.7 per 100,000 from 6.1 per 100,000.[15] (**See Figure 2.4**) It is estimated that the number of ICC cases that would develop each year without screening would be about 12,000 (compared to current approx. 3,000[95]) with about 6000 annual deaths (compared to current approx. 800[96]).[54]

The decline in incidence in the U.K. is almost entirely attributable to SCC, with the crude incidence rates of AC having increased from 2.6 to 3.2 per 100,000 person-years in the period between 1983-1997.[97] The effect of screening on the incidence of AC is less well established than for SCC. These cancers and their

precursor lesions occur in the inner endocervical canal (see **Figure 2.1**) making detection by exfoliation cytology difficult.[56, 98]



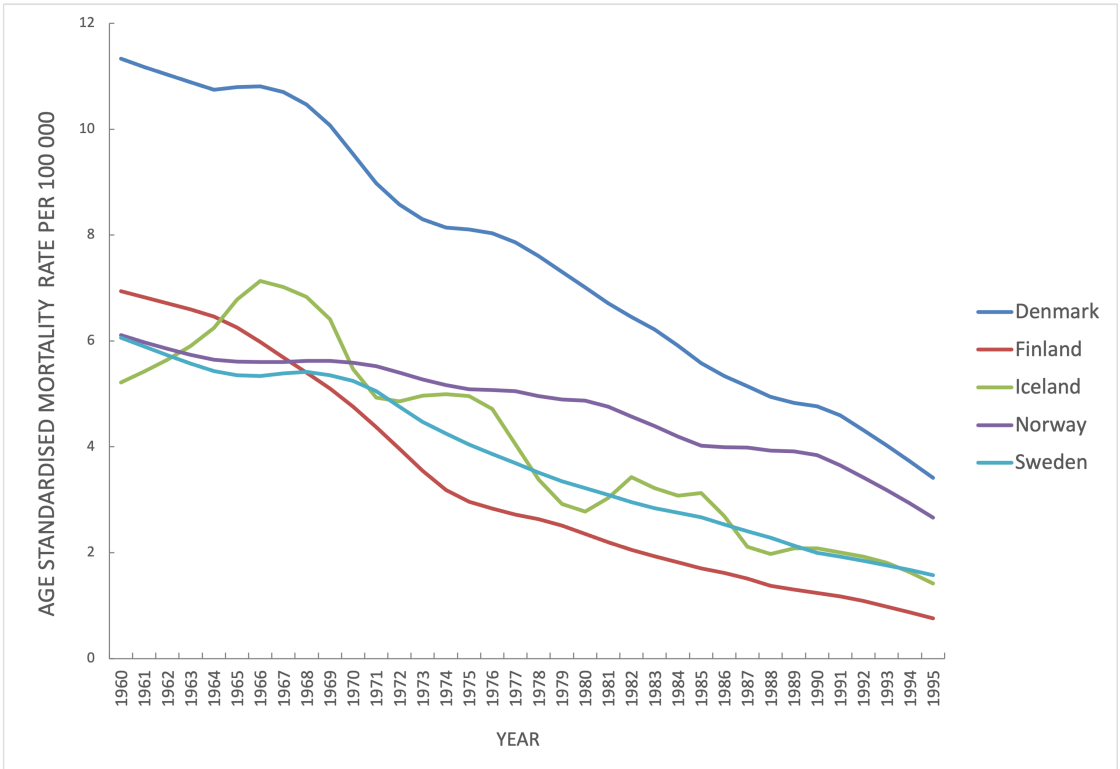

Figure 2.3: Age-standardised (world) incidence and mortality rates of invasive cervical cancer in in the Nordic Countries, all-ages, 1960-1995[99]

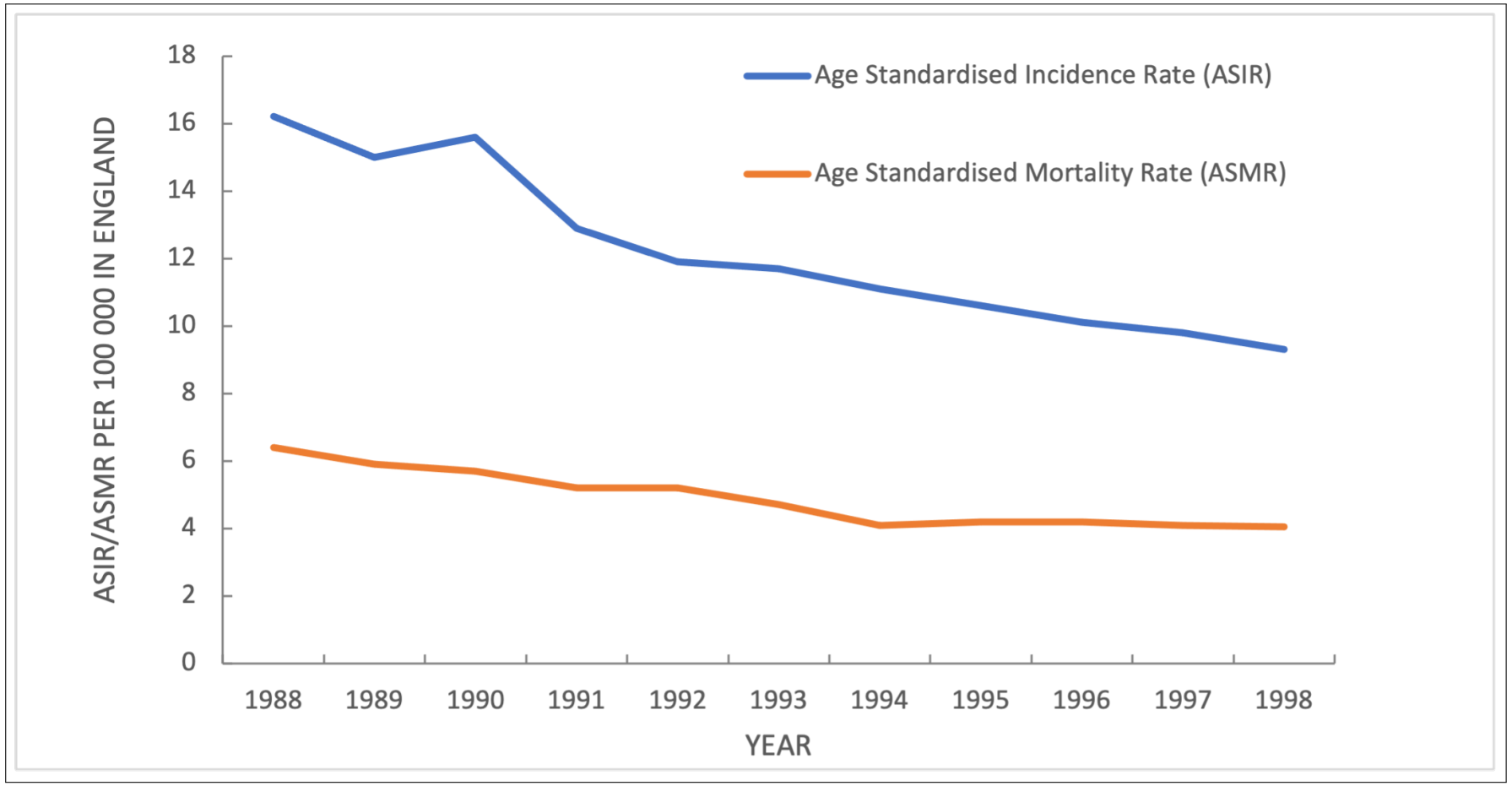

Figure 2.4: Age-standardised (world) incidence and mortality rates of invasive cervical cancer in England, all-ages, 1988-1999[100]

2.4.3 Cervical screening in the United Kingdom: The NHS Cervical Screening Programme

In the U.K., routine cervical screening was introduced in 1966 but had little effect on the incidence of and mortality from cervical cancer owing mainly to problems of organisation.[101] Population-based cervical screening was therefore re-organised under the centrally-organised NHSCSP in 1988. The NHSCSP currently invites all persons with a cervix aged 25-64 years to participate in cervical screening, via primary HPV testing, every 3-5 years (3 years for women under 50 years, 5 years for women over 50 years). Using a call/recall system, an invitation letter (a call) is produced and sent to eligible women registered with a GP; a reminder letter for women who fail to respond within 6 months; and a recall letter at an appropriate time in the next cycle. What follows is a description of NHSCSP screening protocol until 2001 because for the purposes of this thesis, screening history will be derived from the period between the start of the NHSCSP (1988) to recruitment into the Million Women Study (1996-2001). However, NHSCSP policy has undergone several key changes since 2001 and these will be discussed briefly subsequently.

2.4.3.1 NHSCSP: 1988-2001

During this time, the NHSCSP invited all women aged 20-64 for a screening test at a routine interval of 3 or 5 years. The interval was guided by the Health Authority policy operating in the area a woman lived in. Cervical screening was based on the conventional Papanicolaou ("Pap") smear test i.e. cytological testing which involves acquiring a sample of cells for examination under a microscope. The sample is taken from the transformation zone i.e. the area of the cervix where most cancers originate. (see **Figure 2.1**)

Abnormal results were graded based on degree of difference from normal cells (known as dyskaryosis) i.e. mild, moderate or severe dyskaryosis, according to the British Society for Clinical Cytology (BSCC) classification system.[102] Similar to histology, the terminology for cytology results has evolved over time and differs between countries.[102] The BSCC system is compared to other common

classification systems in **Table 2.2**, and correlated to approximate underlying histology in **Figure 2.5**. Correlation of mild, moderate and severe dyskaryosis with CIN1, CIN2 and CIN3 is not exact, however for the most part more severe cytology is correlated with more severe histology.

Table 2.2: Comparison of different cytology terminology systems

Papanicoloau System (1940)[103]	**British Society for Clinical Cytology (1986)**[104, 105]	**European Commission Training Programme**[106]	**The Bethesda System (2001)**[107]
I	Negative	Within normal limits	NILM
	Inadequate	Unsatisfactory due to...	Unsatisfactory for evaluation
II	Borderline nuclear change	Koilocytosis	ASC
	Mild dyskaryosis	Mild dysplasia	LSIL
III	Moderate dyskaryosis	Moderate dysplasia	HSIL
IV	Severe dyskaryosis	Severe dysplasia Carcinoma *in situ*	
V	Severe dyskaryosis /"?" invasive cancer	Severe \?invasive Invasive SCC	SCC
	"?" Glandular neoplasia	Adenocarcinoma *in situ* Adenocarcinoma	AGC or Endocervical AIS Adenocarcinoma

Abbreviations: NILM, negative for intraepithelial lesion or malignancy; ASC, Atypical squamous cells; AGUS Atypical glandular cells; LSIL, Low-grade squamous intra-epithelial lesion; HSIL, High-grade squamous intra-epithelial lesion; AIS: adenocarcinoma *in situ*; SCC, squamous cell carcinoma;"?" query (suspected)

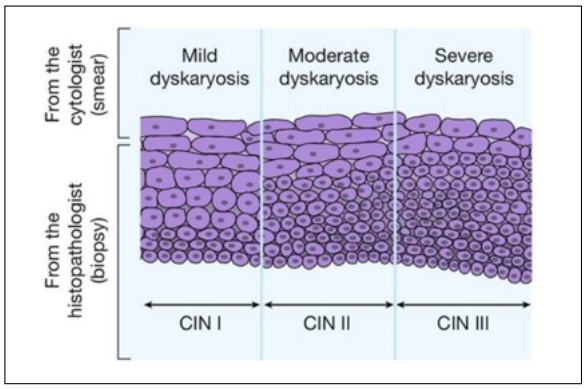

Figure 2.5: Abnormal cervical squamous cell cytology and histologic (CIN) equivalents [108]

Cervical smear results guided recommended subsequent management. During this period (1988-2001), there were four categories of management: routine recall, repeat smear earlier than routine recall, colposcopy and urgent referral as illustrated in **Figure 2.6**.[104] Women who returned negative results were returned to routine recall for an appointment as scheduled within 3 or 5 years. Women who received inadequate smear results or borderline changes results, were directed to repeat smears earlier than routine recall (usually 6 months) and a second repeat may have been requested if results remained equivocal. Women returning the same results after the second repeat smear were then referred for further investigation (colposcopy). After an initial mild dyskaryosis result women were also recommended for early recall, and if these changes persisted, women would be referred for colposcopy. Moderate and severe dyskaryosis smear reports were indications for colposcopy at their first occurrence.

Colposcopy is a continuation of the screening process and contributes evidence as to the nature of the changes present. At colposcopy, if at first examination an appearance consistent with high grade histological abnormality was seen, pathologists might have treated immediately by excisional biopsy i.e. surgical removal of abnormal tissue. If excision was not indicated, tissue samples were generally taken for histology i.e. to diagnose cervical intraepithelial neoplasia. Finally women whose smears were classified "severe dyskaryosis/?invasive cancer (query [i.e., suspected] invasive cancer)" and "?glandular neoplasia (query [i.e., suspected] glandular neoplasia)" were to be urgently referred to a gynaecologist for treatment within 2 weeks.[104]

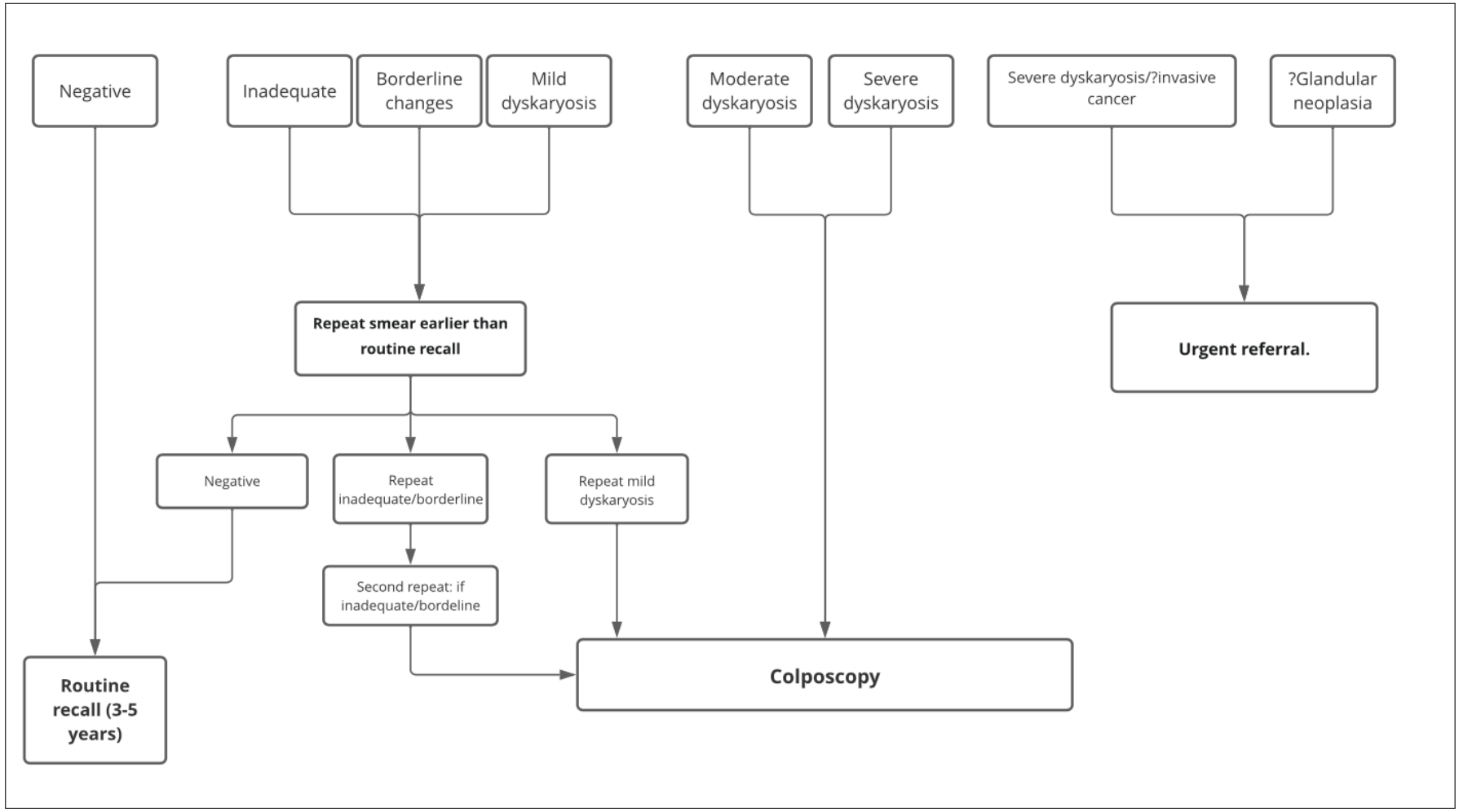

Figure 2.6: Flowchart of NHSCSP cytology result management 1988-2001

2.4.3.2 NHSCSP: 2001 to date

A number of key policy changes have been effected to the NHSCSP since 2001.[101] First, the age range of eligibility for screening changed in 2003 from 20-64 to 25-64 years. This was based on research findings showing no additional impact of starting at age 20 compared to age 25 because majority of abnormalities common in women aged 20-24 are transient HPV associated cellular changes or low-grade abnormalities with a high likelihood of regression.[109, 110] Second, in the same year, the screening intervals were standardised across the programme according to age, with women aged 25-49 years invited every 3 years, and women aged 50-64 years invited every 5 years, as no additional benefit was observed for more frequent screening in older women.[111]

The NHSCSP has also undergone a number of changes with regard to the nature of the screening test offered. In 2008, a new technique offering improved specimen adequacy and reduced screening time [106] known as liquid-based cytology (LBC), was introduced to collect cytology samples in place of conventional Pap cytology.[101] The onset of LBC facilitated HPV triage, the first of HPV related changes in NHSCSP protocol in 2013. This involved triaging low-grade smear abnormalities by HPV status to determine whether to refer to colposcopy i.e. if a woman with was found to have borderline nuclear change or mild dyskaryosis, HPV testing would be carried out and if positive, the woman would be referred for colposcopy.[112] This evolved to the adoption of HPV testing as primary screening in 2019 that is currently in place. In this case, HPV is tested for first and triage done by cytology where HPV is found.[101, 113]

2.5 Cervical cancer epidemiology

2.5.1 Incidence and mortality in the U.K

2.5.1.1 ICC

In the U.K., cervical cancer was the 14th most common cancer amongst women (excluding non-melanoma skin cancer), with an age-standardised incidence rate of 9.7 per 100,000 women,[95] and the 19th most common cause of cancer death amongst women (age-standardised rate 2.6 per 100,000) in the years 2017-2019.[96] As described previously in **Section 2.4.2**, there has been a substantial decline in both the incidence of and mortality from ICC since the start of the NHSCSP in 1988.[14, 15, 54, 95, 96]

Cervical cancer primarily affects younger women, with rapid increase in age-specific incidence from about age 25 years, peaking in women aged 30-34 years, followed by a decline until age 50-54 years with a smaller rise at age 60-64 years as in **Figure 2.7**.[95] This pattern of incidence has been shown to be related to the natural history of HPV infection i.e. infection at the start of sexual activity and the subsequent late-occurring carcinogenic events.[114, 115] However, the apparent age-profile of ICC is as a result of screening which confounds the natural age-specific incidence curve leading to an earlier peak in incidence and providing an explanation for the second peak, representing a return to rates expected in women without the preventive effect of screening as in countries with no access to screening, incidence rises to peak in older women as discussed in **Section 2.5.2**[116]

Mortality rates largely reflect changes in incidence and survival, with peak mortality rates seen in women aged 85-89 years.[96] Survival for cervical cancer has improved over time and for women diagnosed in the UK the current age-standardised 5-year relative survival has been estimated to be 61.4%, 95% CI: 59.8-63.2.[117]

2.5.1.2 CIS

Carcinoma *in situ* (CIS), including CIN3, diagnoses which are detected at screening, are captured as part of NHS central cancer registrations. There are approximately

25,000 cases of CIS detected each year in the U.K., with an age standardised detection rate of 73.5 per 100,000 women in the population.[118] Incidence is also related to age, rising sharply from age 15-19, peaking in women aged 24-29, then dropping sharply thereafter as in **Figure 2.8**.The early peak in CIS is also largely driven by the effect of the NHSCSP, where prevalent cases are detected at the onset of screening.[14, 15]

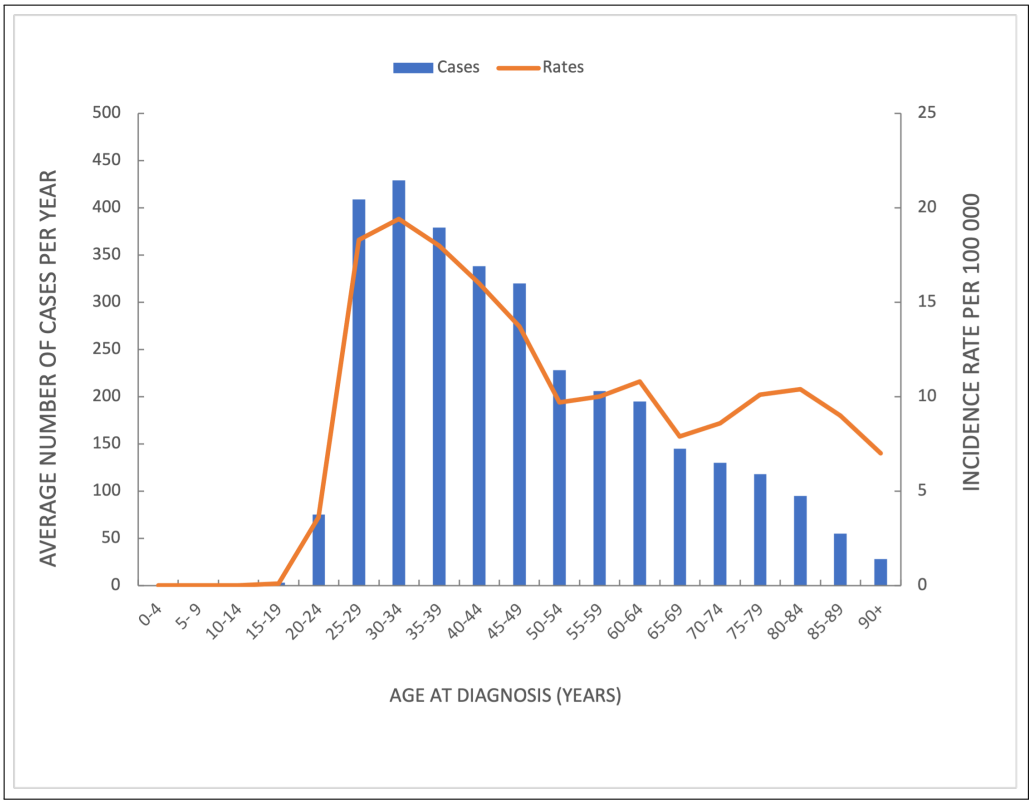

Figure 2.7: Average number of invasive cervical cancer cases per year and age-specific incidence rate per 100 000, U.K 2016-2018[95]

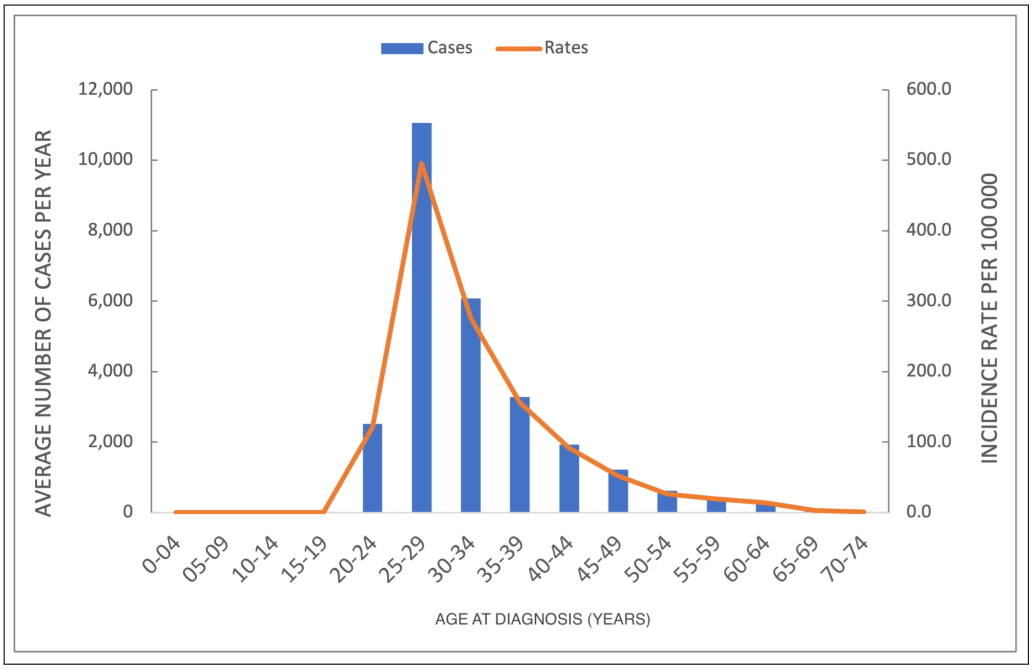

Figure 2.8: Average number of cervical carcinoma *in situ* cases per year and age-specific incidence rate per 100 000, U.K 2016-2018[118]

2.5.1.3 SCC and AC

Incidence and mortality statistics by histological type are no longer released by the Office of National Statistics and the final report released by histo-type was published in 2012.[119] The most common histo-type of ICC in England was SCC, accounting for over two-thirds of ICC diagnoses. Adenocarcinomas were the second most common cervical cancer, accounting for around one-fifth of all tumours. The number of SCCs almost halved between the establishment of the NHSCSP and the mid 2000s, while the number of ACs remained fairly stable with some increases during this period.[119–121]

2.5.2 Global epidemiology

In 2020, cervical cancer was the fourth most common cancer amongst women (excluding non-melanoma skin cancer), with an age-standardised incidence rate of 13.3 per 100,000 women, and the fourth most common cause of cancer death amongst women (age-standardised rate 7.3 per 100,000).[1]

Both cervical cancer incidence and mortality rates show considerable global variation,[122] primarily reflecting the presence/absence of organised screening programmes. (**See Figure 2.9 and Figure 2.10**) Higher incidence and mortality rates are particularly seen in Sub-Saharan Africa, South America and parts of Eastern Europe and lower incidence in Northern Europe, North America and Western Asia.[123] Age-specific incidence rates also show some variation, with incidence rates generally rising at age 25 years to a much later peak of age 55-65 years in lower resource countries where organised screening programmes are not in place (vs. 30-34 years in the U.K.).[116, 123]

Beyond organised screening programmes, other factors have also been suggested to contribute to the contrasts in the global cervical cancer burden. First, a clear positive correlation has been shown between the prevalence of HrHPV in different regions, the main cause of ICC, and respective standardised cervical incidences. In Sub-Saharan Africa where incidence and mortality rates of ICC are among the highest in the world, the prevalence of HPV in women with normal cytology is high,

estimated to be about 24%,[124, 125]. By contrast, in regions where the incidence of ICC is low, a low prevalence of HPV has also been documented[125] such as in the Mediterranean (9.2%) and Western Asia (2.2%) — presumably due to societal influence on sexual behaviour.[27, 126] Further, an increase in the prevalence of other co-factors such as smoking[73] and use of oral contraceptives[6], may be an added factor particularly in younger cohorts.

Cervical cancer therefore continues to be a major public health problem affecting middle-aged women, particularly in less-resourced countries. However, a key concern in the intepretation of GLOBOCAN findings is the quantity of reliable data provided with only 24% of countries providing national incidence data and 44% mortality data of a quality and completeness of registration so as to be directly usable, particularly in sub-Saharan Africa [123] As a result on this, during the course of the DPhil, I have used some of the expertise available in the Cancer Epidemiology Unit to develop a new study I would like to do in Kenya which is included in **Appendix G**. This study seeks to evaluate the data quality in the Nairobi Cancer registry, a population-based cancer registry that provides incidence and mortality data for Kenya. This study hopes to evaluate registry practice towards contributing more reliable estimates both in Kenya and to global comparative assessments such as GLOBOCAN.

2.5.2.1 SCC and AC

Trends in incidence and particularly mortality by type of ICC are less widely reported at the global level. The majority of all cervical cancer cases are SCC (75-90%).[2] The proportion of AC cases varies between 5% and 26% worldwide and is often higher in regions with effective screening programmes and low incidence of cervical cancer,[2] which would reflect that cervical screening is less effective in preventing cervical AC.[86, 98, 127]

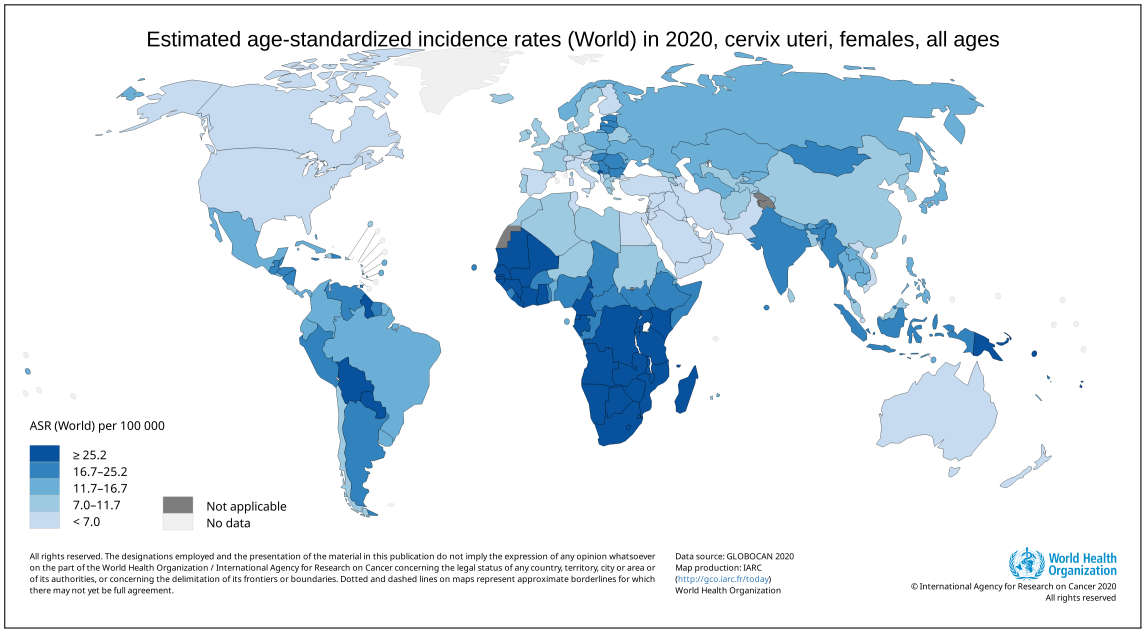

Figure 2.9: Geographical distribution of world age-standardised incidence rates of invasive cervical cancer by country, estimated for 2020 [123]

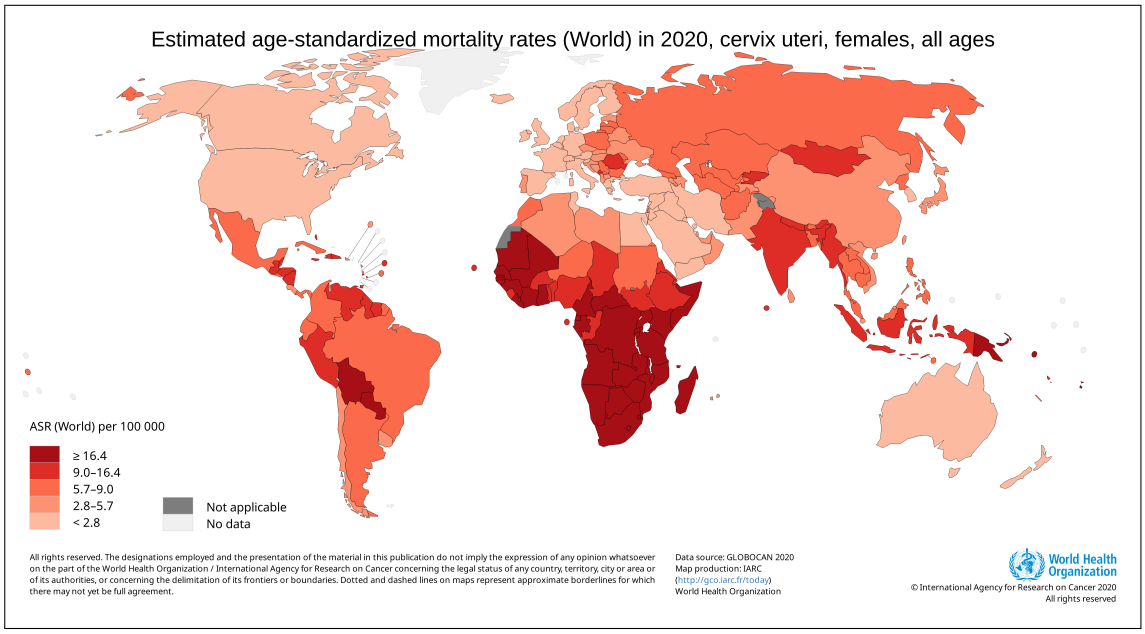

Figure 2.10: Geographical distribution of world age-standardised mortality rates of invasive cervical cancer by country, estimated for 2020[123]

2.6 Conclusion

This chapter has provided an overview of the literature on the aetiology of cervical cancer including introducing evidence on the relationships between reproductive and hormonal factors and the risk of cervical cancer (reviewed more comprehensively in respective chapters). This chapter has also introduced cervical screening in relation to cervical cancer epidemiology which frames the rationale for this thesis. Although several studies have reported on the associations of reproductive and hormonal factors with cervical cancer risk, questions remain about whether, or to what extent, risk is affected by a woman's cervical screening history. To address these questions, this thesis examines the associations of reproductive and hormonal factors with cervical cancer risk, including separately by major histo-type, within a prospective cohort of U.K. women taking into account previous screening history.

Do they use the method because they are bright, or is it the use of the method that makes them bright?

— John Holt

3

The Million Women Study, NHS Cervical Screening Programme records & Methods

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3.1 Introduction

The Million Women Study (MWS) is an on-going population-based prospective study of the health of predominantly post-menopausal women. Originally, the study's main aim was to investigate the risk of breast cancer associated with the use of menopausal hormonal therapy (MHT).[128] The study has subsequently investigated the risks of many other diseases, in relation to other factors including demographic, reproductive, lifestyle, and other behavioural factors. This chapter introduces the design and methods of the MWS, describes the linkage to NHS Cervical Screening Programme (NHSCSP) records used in this thesis and summarises some of the statistical methods used in **Chapters 5-8**.

3.2 Study design

3.2.1 Recruitment and participants

In 1996-2001 (median 1998), participants were recruited via their local NHS Breast Screening Centres. At 66 centres, women aged 50-64 years who were invited for breast mammographic screening also received a MWS recruitment questionnaire. Women were asked to complete the questionnaire and return it at their mammogram appointment. Approximately three million invitations were sent out, and of these about 70% of those receiving invitations attended for screening and around 70% of those attending the screening agreed to participate in the study. The recruitment questionnaire contained information on age, date and place of birth, level of education, home address, body size, lifestyle factors (such as tobacco smoking and alcohol consumption), medical history, reproductive history and detailed questions about use of MHT and the oral contraceptive (OC) pill. Participants provided written consent for participation in the study and follow-up through their medical records. At the end of recruitment, the number of women in the study was about 1.3 million, representing over 1 in 4 women in the UK in the eligible age group.[129] More information on the study is available at the MWS

website (www.millionwomenstudy.org); a copy of the recruitment questionnaire is included in **Appendix A**.

3.2.1.1 Re-survey questionnaires

Since recruitment, re-survey questionnaires have been sent to surviving participants every 3–5 years to update information on exposures either where the exposure status may have changed over time, e.g. MHT use, or to collect new information on an exposure that was not asked about on the recruitment questionnaire such as diet. To date, four different postal re-survey questionnaires have been sent in addtion to the recruitment questionnaire i.e. at median year 2001 (referred to as the "3-year resurvey"), at median year 2006 (referred to as the "8-year resurvey"), at median year 2011 (referred to as the "12-year resurvey"), and at median year 2014 (referred to as the "15-year re-survey"). More information on the study including copies of all questionnaires is available at the MWS website (www.millionwomenstudy.org).

3.2.2 Validation of self-reported information

Validation of self-reported information has been carried out in subsets of participants to examine reporting errors and changes over time in certain characteristics. Good agreement has been found between self-reported information on anthropometric data, reproductive factors and hormone use compared with objective measures or routinely collected health records.[130–132]

3.2.3 Follow-up

3.2.3.1 Linked outcomes

Women in the MWS are followed up through electronic record linkage to routinely collected healthcare and health outcome data in England and Scotland. Follow-up remains virtually complete after 20 years, with about 1% loss to follow-up, mainly due to emigration.

Women are linked to the NHS Central Registers for cancer incidence (including cervical carcinoma *in situ*/CIN3), cause-specific mortality, changes in registration

with the NHS since recruitment in England and Scotland. The English data are administered by the Office for National Statistics/NHS Digital while the Scottish data are provided by the Public Benefit and Privacy Panel (PBPP) for Health and Social Care, part of the NHS in Scotland. Hospital admissions, where relevant, are obtained via the NHS Hospital Episode Statistics in England and Scottish Morbidity Records in Scotland. Linkage to other data include primary care data in England (provided by Clinical Practice Research Datalink) and Scotland (provided by PBPP Scotland), data on cancer outcomes and services in England (provided by UK Health Security Agency [UKHSA], and screening data in England (provided UKHSA). Cervical screening data linkage is described in detail in **Section 3.2.3.2**.

Information that is available in the cancer registration database includes cancer site (coded using the 9th or 10th revision of the International Classification of Diseases, ICD-9 or ICD-10), tumour morphology (coded using the 2nd or 3rd edition of the International Classification of Diseases for Oncology, ICD-O-2 or ICD-O-3), and date of cancer registration. For death registrations and change in registration with the NHS, information is available on date of event (death, emigration or cancellation) and cause of death (coded using ICD-10) where relevant. Information on procedures associated with each hospital admission were coded to the Office of Population Censuses and Surveys classification of surgical operations and procedures, fourth revision (OPCS-4) for procedures (OPCS-3 was used up to 1988).

3.2.3.2 Linkage to cervical screening data

A centrally organised NHS Cervical Screening call/recall system began in 1988 in the UK (see **Chapter 2, Section 2.4.3**), and currently sits on the National Health Application and Infrastructure Services (NHAIS) database (sometimes called the Exeter system). The "Exeter" platform holds information on cervical screening history including screening test date, results and planned follow-up from since the start of the call/recall programme. It also contains information on tests done in private healthcare settings and opportunistic cervical screening tests before 1988 in some cases .

In 2013, permission was obtained to link screening records to women in the MWS which was completed in 2014. Each MWS participant was linked via participant identification numbers matched to name, date of birth and NHS number on screening records. Each time a woman is screened, a standard set of details is recorded on her cervical screening record contained in the NHAIS database. Two key elements of these details are the result code of the test and the action code which indicates recommended action required as a result of the test. Details included the test results code, which in the period for this analysis were recorded as per the BSCC system (**Table 2.2, Chapter 2**). Subsequent action codes indicating recommended action required were also captured: A- routine recall; R-repeat smear at earlier interval and S-suspended, meaning pending further investigation i.e., colposcopy. (see **Figure 2.6, Chapter 2**) However, a limitation of this database is there is no information held on treatment or other outcomes. The database holds records for women living in England, and therefore participants recruited in Scotland were excluded from all analyses in this thesis.

Screening data were initially received and prepared by Dr Roger Blanks and Rupert Alison. They cleaned the data and created 'per woman' variables. Data cleaning principally involved removal of a small number of invalid data values (e.g. tests that occurred prior to 1965, at an age younger than 12, or at non-integer repeat intervals). Prof. Valerie Beral, Dr. Isobel Barnes and I agreed on how to create a "screening history" variable including a record of attendance and a woman's most severe abnormality prior to recruitment, discussed further in **Chapters 4** and **5**. This was based on the work of Dr. Kate Coffey.

Information on Human Papilloma Virus (HPV) status

During the period of assessment of screening history in this thesis (1988- max 2001) the NHSCSP used cervical cytology as a primary screening test.[133] HPV testing only became available for U.K. women in 2013, first as a triage test after cytology testing, and then as a primary screening test in 2019.[134] Information on HPV status was therefore not available for women in the data-set used for this thesis.

Efforts to minimise potential residual confounding by HPV status are discussed in each chapter. It is worth noting, however, that although co-factors such as multiparity have been found to be associated with HPV-linked carcinogenesis, uncertainty remains on where these factors lie on the natural history model or causal pathway (see **Figure 2.2, Chapter 2**). These factors may act in three ways: 1) by influencing the acquisition of HPV infection, 2) by increasing the risk of HPV persistence, and 3) by increasing the risk of progression from HPV infection to CIN3/ICC.[5] For example, it could be that having more children could make a woman more susceptible to HPV infection due to the increased exposure of the transformation zone during pregnancy and delivery.[135, 136] Alternatively, it may also be possible that steroidal effects of pregnancy may dampen the immune response to HPV allowing for persistent infection i.e., pregnancy induced immuno-suppression.[137] However, it may also be that hormone related mechanisms promote the integration of HPV oncogenic proteins increasing the potential for progression.[9, 138] This introduces some methodological challenges in accounting for HPV in analysis of co-factors and the risk of CIN3/ICC, and two main strategies have been adopted to handle this uncertainty in previous investigations. First, is the adjustment for HPV status as potential confounding in analysis. However, these analyses are difficult to interpret because, with the knowledge that the natural history of cervical cancer starts with a persistent HPV infection, women identified as HPV negative who develop cervical cancer may well have been false negatives. The second strategy that has been adopted in accounting for HPV status is restricting analyses to HPV positive women only, which narrows potential mechanisms to those concerned with the development of cancer in the HPV-infected cervix, and is considered the more appropriate way to handle analyses. However, a key issue in this approach is whether a single point measure of HPV status (as in many studies) is a good estimate of a persistent or carcinogenic infection; furthermore, whether a HPV positive test at one point in cases and controls has different meanings. For example, women who have persistent infections are more likely to test positive at a single point in time, and may be more likely to be cases, than those who have short-term transient infections.

Further, in analyses comparing these two strategies, models restricted to HPV positive women yielded stronger magnitude associations than those derived from HPV-adjusted models.[5] This finding is unexpected as lower magnitude associations would be expected in models with less residual confounding. Overall, therefore, questions remain on how to deal with potential confounding by HPV status.

3.3 Ethics

Ethics approval for the Million Women Study was granted by the Oxford and Anglia Multi-Centre Research Ethics Committee (MREC 97/01). The analyses contained in this thesis are all in keeping with the original aims and restrictions of the original ethics approval for the MWS.

3.4 Exposure variables

Exposure variables used in the analyses in this thesis (with the exception of screening history in **Chapters 4** and **5**) are taken directly from participant-reported values from the recruitment questionnaire. (See **Appendix A** for questionnaire) Each results chapter provides details on specific coding of derived exposure variables.

3.4.1 Reproductive factors

Information on reproductive factor, parity, was defined by the number of full-term pregnancies (FTP) i.e. pregnancy that lasted ≥ 26 weeks, as reported in response to the question: "How many children have you had? (please include stillbirths; it is not necessary to include miscarriages)". Women were also asked to record the date of birth of each child, which was used to estimate the woman's age at first FTP.

3.4.2 Hormonal factors

Information on OC use was defined by total duration of ever use as reported in response to the questions "Have you ever used the pill (oral contraceptive)?" and "For how many years in total did you take the pill?"; and time since last use calculated

as the sum of the time elapsed since cessation of use as reported in response to the question “About how old were you when you last came off the pill?"

Information on MHT use was defined as ever use, past use and current use derived from responses to the questions “Have you ever used hormone replacement therapy (HRT)?"; and “Are you now using HRT?" Total duration of ever use for current and past users was derived from responses to the question “For about how many years in total have you used HRT?" and time since last use calculated as sum of the time elapsed since cessation of use as reported in response to the question “How old were you when you last used HRT?" in women who were past users. Updated information on these exposures of MHT were obtained at 3 and 8 year resurveys in response to similar questions.

3.5 Outcome ascertainment

Participants were followed up for outcomes: incident invasive cervical cancer and incident CIN3 registrations (International Classification of Diseases 10th Edition code C53 and D06 respectively) through linkage to the NHS cancer registries. Cases were defined as women who developed ICC or CIN3 after the date of recruitment and the end date of follow-up for incident cancer for all regions which was 31st December 2018.

For analyses split by histological subtype, the cases of cervical cancer were divided into groups based on the coding system of the International Classification of Diseases of Oncology-3rd edition (ICD-O-3) as reproduced in *Cancer Incidence in Five Continents, Volume XI.*[139] Invasive cervical cancer was split into squamous cell carcinoma (ICD-O-3 codes 8070/3-8072/3, 8051/3, 8052/3, 8083/3 ,8082/3, 8076/3) and adenocarcinoma (8140/3, 8263/3, 8380/3 ,8310/3, 8441/3, 8574/3, 8260/3, 8323/3, 8384/3, 8480/3, 8481/3).

3.6 Statistical analyses

Each of the individual results chapters includes a description of the methods used; some common features of the statistical analyses are outlined here.

3.6.1 Exclusions

Of the 1 364 308 women available for this study, women were excluded if they had no matched screening records (n=798) i.e., had no traceable records in *all* linked screening data available or were recruited in Scotland (n=117,167) as screening data was only available for England. Women who were over 65 at recruitment into the MWS (n=44,298) and women who reported having had a hysterectomy (n=307,755) were also excluded as they would not be eligible to be invited to attend for screening, and in the case of hysterectomy would not be at risk of developing CIN3 or ICC. Women with an invasive cancer registration (excluding non-melanoma skin cancer (ICD-10 code C44) prior to recruitment into the MWS were also excluded (n=20,102) as they may have changed screening or health behaviour as a result of their diagnosis. Women with smears recorded with missing information on test dates or results (n=13) were also excluded. For analyses for the risk of CIN3, women with CIN3 registrations prior to recruitment(n=6,967), who may have changed health behaviour, and women with no test record (n=24,338), who are unlikely to attend for future screens[140] and therefore would not have CIN3 detected, were also excluded. For analysis of each main exposure of interest, women were excluded if they had missing data on that variable.

3.6.2 Multivariable regression models

Women contributed person-years from the date of recruitment until the earliest of the date of invasive cancer registration (excluding non-melanoma skin cancer, ICD-10 code C44), date of death or loss to follow-up, or the last date of follow-up (31 December 2018). For analysis of risk of CIN3, follow-up was additionally censored at a woman's 65th birthday when she would no longer be eligible for

routine screening on the NHSCSP as a proxy for last test date as screening history beyond recruitment into the MWS was not considered in these analyses

Cox proportional hazard regression models were used to calculate hazard ratios (referred to as relative risks [RR]) and corresponding 95% confidence intervals (CI) for CIN3/ICC associated with each exposure of interest. Time on the study was the underlying time variable. Graphical methods were used to check for violation of the proportional hazards assumption.

All analyses were stratified by year of birth(<1930, 1930, 1931...1949, 1950, 1950+) and year of recruitment (1996...2000, 2001+). Simple descriptive statistics (e.g. means and percentages) were used to compare associations between various personal factors and both the main exposure i.e., reproductive and hormonal factors, and the outcome i.e., cervical cancer. Variables that were associated with both the exposure of interest and associated with the outcome were included in regression models as possible confounders. Other factors which have been considered possible confounders in other investigations were also considered as covariates *a priori* even if they were not risk or preventative factors for the outcome in dataset. For example, variables such as education and socioeconomic status which may be markers of a wide range of factors related to cervical cancer risk were also treated as confounders in the analysis. Information on all adjustment variables (except screening history) was taken from the recruitment questionnaire and was missing or reported as unknown for <1% for all the adjustment variables except BMI (5%), education (3%) and age at first FTP (3%). To ensure that the same women were compared in all analyses, for each adjustment variable missing values were assigned a separate category.

Adjustment variables used in Chapter 5-8 included the following: region of residence, socioeconomic status assessed via Townsend deprivation scores, education, smoking status, body mass index (BMI), parity and age at first birth, use of oral contraceptives, use of menopausal hormone therapy and for individual screening history. The Townsend index is the favoured deprivation measure among UK health authorities and is a measure of material deprivation measured for the population of a given area incorporating four variables: unemployment, non-car ownership,

non-home ownership and household overcrowding.[141] Adjustment variables used in multivariable models are listed in each of the individual results chapters.

Adjustment variables were coded as follows: region of residence (9 regions corresponding to the areas covered by the cancer registries: Oxford, East Anglia, South West, Thames, West Midlands, Northern and Yorkshire, Trent, North West [Mersey] and North West [Manchester/Lancashire]); socioeconomic status assessed via deprivation scores (tertiles based on the Townsend index); education (tertiary qualifications [college or university], secondary qualifications [A levels or O levels usually obtained at 18 and 16 years of age, respectively], technical qualifications [nursing, teaching, clerical or commercial], no educational qualifications [either completed compulsory schooling with no qualifications or did not complete compulsory schooling (upto 15 years)]); smoking status (never, past, current); body mass index [BMI] <25, 25-29, 30+kg/m^2); parity and age at first birth (nulliparous, parous 1-2 and <25 years, parous 1-2 and 25+ years, parous 3+ and <25 years, parous 3+ and 25+ years); use of oral contraceptives [OC] (never, ever); use of menopausal hormone therapy [MHT] (never, ever) and for individual screening history (non-attenders, attenders $\leq$5 years before recruitment[no abnormality, any abnormalities], attenders >5 years before recruitment [no abnormality, any abnormalities]). Adjustment variables used in multivariable models are listed in each of the individual results chapters.

Tests of heterogeneity in the relationship between ICC and each exposure of interest by histo-type, i.e. SCC and AC, were performed using a competing risks approach described by Lunn and McNeil.[19] This method involves the duplication of the data by the number of outcomes, in this case the 2 major histo-types, and allows for testing of heterogeneity between the two outcomes in prospective analyses.

All analyses were performed in STATA version 17.0 (Stata Corp, LP, College Station, TX). Figures were drawn in R, using Matthew Arnold's "Jasper" package.

I am not free while any woman is unfree, even if her shackles are very different from my own

— Audre Lorde

4

Personal factors affecting non-attendance for organised cervical screening

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4.1 Introduction

Organised cervical screening programmes such as the NHS Cervical Screening Programme (NHSCSP), have reduced invasive cervical cancer incidence and mortality via the early detection and treatment of precursor lesions.[54] Maintaining high coverage, i.e. high attendance of eligible persons at screening is considered a pre-requisite for effective organised screening.[17] There is some evidence that U.K. women who do and do not attend for organised cervical cancer screening are different.[142–148] Previous studies have found that the likelihood of not attending screening is higher among older women[142, 147] and women of low socio-economic status (SES).[142, 145, 148] Little is known about what other factors characterise non-attenders for screening in England.

In this chapter, I present the findings of a narrative review of previous evidence on personal factors associated with attendance for cervical screening in the U.K. from the start of the NHSCSP (1988). I then report on an investigation of personal factors influencing cervical screening non-attendance in England using a unique dataset, combining the Million Women Study (MWS) with linked NHSCSP records from the start of the NHSCSP to recruitment into the cohort in 1996-2001, as described in the previous chapter. Specifically, this study 1) compares non-attenders to attenders for the NHSCSP in relation to potential differences in socio-demographic, behavioural, reproductive and hormonal factors 2) compares poor-attenders to good attenders for the NHSCSP in relation to the same personal factors.

4.2 Literature Review

4.2.1 Objectives

The aim of this review is to summarise previous evidence on factors associated with non-attendance for cervical screening in the U.K. In particular, the following questions were addressed in this review: 1) Which personal factors are associated with non-attendance for cervical screening? 2) Which personal factors are associated with poor attendance for cervical screening?

4.2.2 Methods

I conducted a literature search of online database PubMed to summarise the evidence on personal factors influencing non-attendance for organised cervical screening through the NHSCSP in the U.K. i.e., only during the period from April 1988-1 Jun 2022. The date restriction was selected to limit the review to English studies carried out from the re-organisation of the NHSCSP. Studies prior to the establishment of the re-organised NHSCSP in 1988 are excluded.

The search terms included in this review were a combination of "cervical screening", "pap smear", "attendance", "participation", "determinants of attendance", "predictors of attendance", "characteristics of attenders", and "United Kingdom", "England", "Great Britain." Additional papers were identified by searching reference lists of identified papers. All identified papers were reviewed for relevance based on titles and abstracts, which were then exported to Mendeley bibliographic database manager and full texts retrieved and reviewed.

Any original quantitative studies published in peer-reviewed journals examining the association between screening non-attendance or poor attendance for cervical screening in relation to the following personal factors were included: socio-demographic (age, SES and education), behavioural (smoking status and body mass index [BMI]), reproductive (parity and among parous women: number of full-term pregnancies [FTP] and age at first FTP) and hormonal factors (use of oral contraceptives [OC] and menopausal hormone therapy [MHT]). Studies that

reported any non-attendance/poor attendance for organised screening determined by health service records or self-report were included.

Details on study characteristics including study size, region, study participants, screening history assessment and definition, and adjustment for potential confounding were extracted. Maximally adjusted measures of non-attendance or poor attendance in relation to socio-demographic, behavioural, reproductive and hormonal factors were extracted from each article and are presented.

A separate search was also conducted including all organised cervical screening programmes (beyond England) which aim to detect and treat cervical cancer or cervical pre-invasive abnormalities before they become clinically apparent. Similar inclusion criteria were applied and details extracted from the studies are included for comparison in **Table B.1 Appendix B**.

4.2.3 Results

The search identified 48 papers, of which 2 were duplicates. I excluded 36 papers based on title and abstract review, leaving 10 articles which were examined in full text review. No additional articles were identified from reference lists. Three studies were excluded from this review as they used qualitative methods. A total of seven studies were eligible for inclusion in this review.[142–148] Study characteristics and results are presented in text and in **Table 4.1**

The studies included women who were aged between 20 and 74 years. Study sizes were variable ranging from 580 to 72,613 women. Screening history was determined by self-report in all studies except one[142] that used linked screening programme records. The definitions of non-attendance and the proportion of non-attenders were varied across the studies as detailed in **Table 4.1**. Women were classified as non-attenders if they never had a screening test in some studies[142, 144, 145] or if they were overdue for their screening tests[143] or a combination of both.[146, 147] In one study, non-attendance was also defined based on a woman's intention to be screened in future and women who were up-to-date with tests but did not intend to attend future screening tests were classified as non-attenders.[148]. Response rates

to interviews/questionnaires in these studies was also varied ranging from about 50% to 70%. The reported proportion of non-attenders was low in most studies (<10%). Coverage in the U.K. i.e. the proportion of women eligible for cervical screening who were screened adequately within the recommended interval, was around 80% during the study periods included i.e., 1990-1999.[149]

The studies provided evidence on sociodemographic factors, age, SES and education. To the best of my knowledge, there was no evidence from the U.K. on potential associations with any of the selected behavioural, reproductive and hormonal factors. The degree to which the studies accounted for confounding was also highly variable with the least reporting unadjusted results[148] while others adjusted for a combination of other variables including SES, ethnicity, education, income, GP practice level variables and attitudinal variables as presented in **Table 4.1**

4.2.3.1 Socio-demographic factors

Age

Six studies reported associations between non-attendance and age.[142–144, 146–148] Of these, two studies reported significantly higher odds for non-attendance with older age (Webb *et al.* = OR: 1.66, 95% CI: 1.48-1.86 for age 60-64 vs.<50 years; Marlow *et al.* 2015= OR: 1.95, 95% CI: 1.21-3.15 for age 51-60 vs. 30-40 years).[142, 147] One study reported significantly lower odds of non-attendance with older age from unadjusted models (Marlow *et al.* 2017= OR: 0.57, 95% CI: 0.44-0.72 for 55-64 vs. 25-34 years).[148] Three studies reported no significant associations between non-attendance and age.[143–146]

Socioeconomic status (SES)

Five studies reported associations between non-attendance and a range of SES indicators,[142–145, 148] with two studies reporting no significant associations between non-attendance and SES based on total income.[143, 144] The remaining three studies reported higher odds of non-attendance for women of lower SES backgrounds as indicated by the Townsend deprivation index[141] (Webb *et al.* = OR: 1.27, 95% CI: 1.11-1.45 for Townsend most vs. least deprived)[142] and

also when comparing women in lower vs. higher grade occupations (Moser *et al.* = OR: 1.51, 95% CI: 1.03-2.20 for women in routine/manual vs. intermediate occupations[145]; Marlow *et al.* 2017 = OR: 3.13, 95% CI: 2.33-4.34 for women in lowest grade casual vs. professional occupations.[148]

Education

Five studies reported associations between non-attendance and education.[143–147] Of these, 2 studies reported significantly higher odds of non-attendance for women with lower vs. higher educational qualifications (Marlow *et al.* 2008= OR: 1.82, 95% CI: 1.18-2.78 for no qualifications vs minimum qualifications (General Certificate of Secondary Education [GCSE]),[144] Moser *et al.*= 1.79, 95% CI:1.01-3.13 for no qualifications vs degree or equivalent.[145] By contrast, one study reported that compared to women with some education (completed education aged 15-18), there were significantly lower odds for non-attendance for with higher education i.e. completing education at ages 19-25: Sutton *et al.* 2005= OR vs. 15-18: 0.40, 95% CI:0.22-0.70 for ages 19-25, but no significant associations with non-attendance for women completing education at older ages [25+] OR: 0.58, 95% CI: 0.16-2.09.[143] This pattern was similar in the final two studies although these also did not reach statistical significance.[146, 147]

4.2.3.2 Behavioural, reproductive and hormonal factors

I found no evidence from the U.K. on the selected behavioural factors influencing non-attendance for cervical screening included in this review.

4.2.4 Discussion

Very few studies have investigated the personal characteristics of women who do and do not attend for routine cervical screening in the U.K. after the re-organisation of the NHSCSP in 1988 and to my knowledge, only the seven studies included here have been published on this relationship.[142–148] Broadly, the evidence suggests higher non-attendance in older women and women from lower socioeconomic backgrounds. The evidence on the association between education level and non-attendance was inconsistent, with some studies suggesting that non-attenders were more likely to have lower education[144, 145] while in others,[143, 146, 147] there was some suggestion that women with higher education had higher odds of non-attendance. As far as I am aware, there is no published evidence for the specified behavioural, reproductive and hormonal factors in the U.K.

The studies in this review, however, have important limitations. First, in most studies screening attendance was determined based on self-report, and is therefore subject to reporting errors and participation bias. Self-reported screening histories have been shown to be overestimated and validation studies using screening record registries generally show poor agreement. [150, 151] Further, personal factors have also been shown to influence validity of reporting and for women with certain personal characteristics, such as lower SES or in minority ethnic groups, self-reported estimates of screening may be even more misleading.[152] Second, the studies included had a range of definitions of screening non-attendance including women who had never had a cervical screening test, women who had had a test before but were overdue for attending screening test or a combination. It is therefore possible that the results reported may have been subject to some misclassification. For example, in the study by Marlow *et al.* published in 2017, non-attenders were a mixed group of women including those who reported having never been screened; those who had attended for screening but were overdue; and those who were up-to-date but reported not intending to attend in future or were unsure.[148] This study reported that overall, increasing age was associated with a lower odds of non-attendance (OR: 0.57, 95% CI: 0.44-0.72 for 55-64 vs. 25-34 years). However,

when looking at results in separate non-attender groups, the odds of non-attendance were lower with increasing age in women who were unaware of screening ("true non-attenders") (OR: 0.35, 95% CI: 0.23-0.54 for 55-64 vs. 25-34 years) although there were higher odds of non-attendance with increased age in women who decided not to be screened further (OR: 3.86, 95% CI: 2.24-6.66 for 55-64 vs. 25-34 years). Consequently, overall findings may have been misleading. It may therefore also be possible that in other studies where definitions of non-attenders included some attenders, any associations between personal factors and non-attendance reported may have been blurred to the null.[146, 147]

Studies were also limited with respect to collection of information on exposures i.e. personal factors. First, where routine administrative databases were used to collect personal information,[142] the range of exposures examined was limited and also consequently lacking in detailed information to adjust for relevant confounding. Personal information collected from routine national surveys was similarly limited in terms of factors assessed and potential confounding. Poor or unknown response rates to national surveys, with little known about non-responders and how they may differ from responders, is also a limitation in these studies. Although some studies reported weighting the data to correct for non-response,[144, 145, 148]some bias may remain if non-responders varied by factors not included in the weighting. In one study,[143] it was reported that non-responders differed from responders by SES, and it is possible that this may have been an issue in other studies.

Evidence on these associations is also limited beyond the U.K. but conclusions on socio-demographic factors have been broadly similar (see **Appendix B Table B.1**). Higher non-attendance has been reported in older women[153, 154]; women with lower SES [154–159] and women with lower levels of education.[153, 155–158, 160] Few studies have looked at behavioural, hormonal and reproductive factors; and obesity,[158] smoking,[155, 160, 161] nulliparity,[153, 156, 158–160] and non-use of OC[160] have been reported to be associated with higher non-attendance. I found no published evidence, in the U.K. or beyond, on potential associations between non-attendance and age at first FTP or use of MHT.

The linkage of the MWS and the NHSCSP screening records therefore provide for the first time a comprehensive dataset to investigate potential associations in England. By using the MWS which has collected detailed information on a wide range of socio-demographic, behavioural, reproductive and hormonal factors; and the NHSCSP which provides objective data on screening history, there is now the opportunity to overcome some of the shortcomings of previous studies. The remainder of this chapter reports findings from a study of over 800,000 women with detailed personal information and linked screening history during the period of 1988-2001.

4.3 Factors associated with non-attendance for cervical screening in England

4.3.1 Objectives

The analysis that follows will examine the odds of non-attendance and poor-attendance in relation to sociodemographic, behavioural, reproductive and hormonal factors of interest.

4.3.2 Methods

4.3.2.1 Study cohort

Data were obtained from the MWS with linked NHSCSP records. The methods of recruitment, data collection, follow-up, and ascertainment of cervical cancer for the MWS; and extraction and linkage with NHSCSP screening data have been described in detail in **Chapter 3**.

4.3.2.2 Exposures

Factors influencing non-attendance at cervical screening were derived from information collected via MWS recruitment questionnaires in 1996-2001. Four categories of variables were defined from self-reported characteristics: sociodemographic, behavioural, reproductive and hormonal factors. Sociodemographic factors included age at recruitment (<55, 55-60, 60-64 years), socio-economic status assessed from deprivation scores (tertiles based on the Townsend index[141]) and education. Education was divided into four categories: tertiary qualifications (college or university), secondary qualifications (A levels or O levels usually obtained at 18 and 16 years of age, respectively), technical qualifications (nursing, teaching, clerical or commercial), and no educational qualifications (completed compulsory schooling with no qualifications or did not complete compulsory schooling). Behavioural factors included smoking status (never, past, current) and body mass index (<25, 25-29, 30+kg/m^2). With respect to reproductive factors I considered parity (nulliparous, parous) and among parous women the age at first FTP (<18, 18-20, 21-24, 25+

years) and number of FTPs (1-2, 3-4, 5+). For hormonal factors, I included OC use (never, ever) and use of MHT (never, ever).

4.3.2.3 Outcome

The main outcome of interest was screening attendance which was ascertained from NHSCSP records during the screening history period, defined as the period between the start of the NHSCSP (1st April 1988) and recruitment into the MWS (1996-2001), and was classified in two ways. First, women were classified as "attenders" or "non-attenders" based on a record of a test in the NHSCSP. Women were categorised as "attenders" if they had at least one test during the screening history period and as "non-attenders" if they had no tests recorded during the same period. Women were also categorised as "non-attenders" if they *only* had a record of an inadequate test result, with no further tests and no referral to colposcopy. This is because tests results recorded as "inadequate" should have resulted in repeat testing within 6 months and referral to colposcopy after a third consecutive inadequate test.[162] (**see Figure 2.6**)

Second, women who were attenders were classified based on the time since their last test within the screening history period as a proxy for frequency of attendance: ≤ 5 years before recruitment or >5years before recruitment. The five-year cut-off was selected because prior to 2003, the NHSCSP invited women at intervals of 3 or 5 years depending on local policy.[133] (See **Chapter 2, Section 2.4.3.2**) It is therefore expected that during the screening history period women attending regularly i.e., as recommended by the NHSCSP, should have had the opportunity to have attended for screening at least once within 5 years of baseline (recruitment to MWS). Further, during this time, NHSCSP coverage statistics i.e., percentage of women in the population who are eligible for screening who were screened adequately, were estimated based on a five-year period.[163]. Consequently for the remainder of this chapter, women with tests taken ≤ 5 years before recruitment will be referred to here as "good attenders" and those with tests taken >5 years before recruitment will be referred to as "poor attenders"

4.3.2.4 Statistical analyses

Logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI) of non-attendance vs. attendance for cervical screening by age at recruitment, SES, education, smoking status, BMI, parity, OC use, and MHT use. Analyses were first minimally adjusted for age at recruitment (<55, 55-60, 60-64 years) and region of residence (9 regions corresponding to the areas covered by the cancer registries: Oxford, East Anglia, South West, Thames, West Midlands, Northern and Yorkshire, Trent, North West [Mersey] and North West [Manchester/Lancashire]), then fully adjusted for all other factors in all women, as appropriate. Logistic regression was also used to calculate ORs (95% CI) of non-attendance for number of FTPs and age at first FTP among parous women only. In this case, minimally adjusted models were adjusted for age at recruitment, region of residence only and fully adjusted models, were then further adjusted for all personal factors including reciprocal adjustment for number of FTPs or age at first FTP, among parous women only. These methods were repeated to estimate ORs and 95% CIs for poor attendance compared to good attendance by each personal factor.

Sensitivity analyses were performed repeating all analyses using only those with complete information for each variable. To assess the choice of a 5-year screening window, a sensitivity analysis was conducted considering a 3-year window as invitation intervals were varied across Health Authorities (3 or 5 yearly) during the screening history period.

4.3.3 Results

4.3.3.1 Recruitment characteristics

This analysis included a total of 874,175 women who were eligible to have been invited for cervical cancer screening in England. Of these, 97% were attenders (n=849,837) and 3% were non-attenders (n=24,338). Within attenders, 95% (n=808,992) last attended ≤ 5 years before recruitment i.e., were good attenders and 5% (n=40,845) last attended >5 years before recruitment i.e., were poor attenders. Overall, women had a mean age (SD) of 45.5 (4.5) at the start of the NHSCSP (1988) and 56.1 (4.4) at recruitment (1996-2001).

Table 4.2 shows the recruitment characteristics for attenders and non-attenders, and for poor vs. good attenders. At recruitment, 48% of non-attenders were nulliparous compared to 10% in attenders. When compared to attenders, women who were non-attenders reported far less use of OCs (31% vs 61%) and MHT (18% vs 45%). Differences were also observed for age, SES and BMI between non-attenders and attenders; non-attenders were generally, from lower socioeconomic backgrounds and had higher BMI at recruitment compared to attenders. At recruitment, poor attenders were more likely to be nulliparous compared to good attenders (19% vs. 10%). They were also less likely to have used OCs (52% vs. 62%) and MHT (28% vs. 45%) and were also generally from lower socioeconomic backgrounds, had higher BMI and were more likely to be current smokers at recruitment compared to good attenders.

4.3.3.2 Factors associated with NHSCSP attendance in England in the Million Women Study in 1988-2001

Odds ratios for non-attendance compared with attendance (middle panels); and poor attendance compared with good attendance (right panels) in relation to socio-demographic factors are shown in **Table 4.3**, behavioural factors are shown in **Table 4.4**, hormonal factors are shown in **Table 4.6** and reproductive factors are shown in **Table 4.5**. ORs from minimally adjusted models were broadly similar to ORs from fully adjusted models, which are reported in the following text.

Sociodemographic factors

Older age, lower SES and higher educational qualifications were all associated with higher non-attendance (OR for 60-64 vs. <55 years = 1.29, 95% CI: 1.25-1.33, OR for most vs. least deprived tertile = 1.41, 95% CI: 1.37-1.46 and OR for tertiary vs.no educational qualifications 1.29, 95% CI: 1.24-1.35). These effects were broadly similar when comparing poor vs. good attendance, although slightly stronger for age and slightly weaker for SES and educational qualifications. (**Table 4.3**)

Behavioural factors

Women with a higher BMI and current smokers were more likely to be non-attenders (OR for BMI 30+ vs. <25kg/m^2 =1.46, 95% CI: 1.41-1.52 and OR for current vs. never smokers = 1.18, 95% CI: 1.14-1.22). However, past smokers were less likely to be non-attenders when compared to never smokers. (OR for past vs. never smokers = 0.85, 95% CI: 0.82-0.88).

These effects were broadly similar when comparing poor vs. good attenders, although slightly stronger for both BMI and smoking status (OR for BMI 30+ vs. <25kg/m^2 =1.59, 95% CI: 1.55-1.64 and OR for current vs. never smokers = 1.55, 95% CI: 1.51-1.59) (**Table 4.4**)

Reproductive factors

One of the largest effects was seen for parity. (**Table 4.5**) When compared to parous women there were substantially higher odds of non-attendance versus attendance in nulliparous women (OR for nulliparous vs. parous = 7.02, 95%CI: 6.84-7.22). This pattern was similar although attenuated when comparing poor vs. good attenders (OR for nulliparous vs. parous = 2.15, 95% CI 2.10-2.21)

Among parous women, there was some evidence of higher non-attendance with higher number of FTPs, OR for 5+ vs 1-2 FTPs = 1.22, 95%CI: 1.13-1.32. This effect was also significant when comparing poor vs. good attendance (OR for 5+ vs 1-2 FTPs= 1.35, 95%CI: 1.28-1.42).

Women who were younger at first FTP (<18 years) were 17% more likely to be non-attenders compared to those aged 21-24 (OR = 1.17, 95%CI: 1.05-1.30). Women who were younger at first FTP were still significantly more likely to be poor vs. good attenders (OR for first FTP at <18 vs. 21-24 years = 1.07, 95% CI: 1.00-1.15).

Hormonal factors

As presented in **Table 4.6**, use of OCs and MHT was associated with lower odds of non-attendance (OR for ever vs. never use = 0.43, 95% CI: 0.41-0.44 and OR for ever vs. never = 0.31, 95% CI: 0.30-0.32 for OC and MHT use respectively). Although attenuated, the pattern of effects were broadly similar when comparing poor vs good attendance (OR for ever vs. never OC use = 0.82, 95% CI: 0.80-0.84 and OR for ever vs. never MHT use = 0.50, 95% CI 0.49-0.51).

4.3.3.3 Sensitivity analyses

The restriction of analyses to women with complete information on all personal factors (n=789,518), did not materially alter the observed associations of non-attendance and poor attendance (**Appendix B, Table B.2**). Broadly, associations with personal factors remained statistically significant, albeit attenuated, when time since last screen was altered to $\leq 3/>3$ years before recruitment (**Appendix B, Table B.3**, right panels). Attenuation of the strength of estimates suggests using a 3-year window may have been subject to some misclassification of attenders/good-attenders suggesting choice of 5-year window as reasonable.

4.3.4 Discussion

4.3.4.1 Overall findings

In this large cross-sectional study of English women, the highest odds of non-attendance for cervical screening were seen in nulliparous women. Women who were older; from lower socioeconomic backgrounds; had higher educational qualifications; were current smokers; and were obese were also more likely to be non-attenders. Among parous women, women who were younger at first FTP (<18 years) and grand-multiparous women i.e. women with 5+ FTPs [164] were more likely to be non-attenders. By contrast, women who reported ever use of OCs or MHT were less likely to be non-attenders.

Broadly similar patterns were seen in the analyses on time since last test, and all personal factors were also significantly associated with poor vs. good attendance, suggesting a strong association between attendance for screening and personal factors. It is of note that these analyses have reported differences in screening attendance history according to several known risk factors for cervical cancer, namely smoking, parity and OC use, for the first time in England. As far as I am aware, the association between screening history and age at first FTP reported in this study has also not been reported elsewhere. Given the strong association between screening and risk of cervical cancer,[16] the potential confounding effect of screening history on the risk of reproductive and hormonal risk factors is considered in **Chapters 6-8**.

4.3.4.2 Comparison with previous evidence and possible mechanisms

These analyses have shown that personal factors are significantly associated with both non-attendance and poor attendance. Previous evidence has been limited in this regard, with studies reporting on these associations in either non-attenders only,[142, 144, 145] poor attenders only[143, 147] or grouping non-attenders and poor attenders,[146, 148]. As such, misclassification of attendance status may have influenced findings in these studies.

Differences in screening history according to known risk factors have been reported previously outside of England for smoking,[160, 161] multiparity,[156–160]

and OC use.[160]. These associations are consistent with the hypothesis that there may be an inverse association between attendance for screening and level of risk i.e., those at higher risk of cervical cancer may be less likely to attend such as current smokers or multi-parous women.[165] These findings may indicate a need for targeted interventions, and further work remains to be done.

Sociodemographic factors

Previous studies, in England and beyond have reported inconsistent findings on the association between age and screening attendance; with directly proportional,[142, 147, 153, 154] inversely proportional,[148, 155, 156] and null[143–146, 160] associations reported between increasing age and non-attendance. The results presented in this chapter are similar to studies reporting higher odds of non-attendance with increasing age. Most previous studies compare older women (55+ years) to much younger women (<35 years) and are therefore not directly comparable with the analysis of older women presented here.[143, 144, 146–148] However, the findings in this study were similar to those of Webb *et al.,* which also focused on older women.[142] It is not surprising that age was significantly associated with non-attendance for screening in this older cohort. Studies suggest that some older women may perceive cervical screening as a gynaecological service related to current sexual activity therefore only relevant to younger women.[166, 167]

This chapter, like many previous studies,[142, 145, 148, 154–159] has reported that lower SES is associated with higher non-attendance. Lower attendance for screening in lower SES backgrounds has been documented as a problem in the NHSCSP, both at area-level and individual level.[165, 168] In contrast to these findings, however, it has been previously suggested that attendance to organised screening in England may be more clearly affected by ethnicity versus SES,[145] with women who live in more ethnically diverse communities reported to be slower to attend than women of lower SES.[169] The vast majority of women in the MWS are of white ethnicity (96%) suggesting an independent role of SES and further

investigation in more ethnically diverse study populations is therefore warranted to consider potential confounding.

Contrary to previous findings in England and beyond,[144, 145, 154–159] I found that in fully adjusted models, women with tertiary educational qualifications (degree or higher) were more likely to be non-attenders compared to those with lower educational qualifications. The reason for this difference is unclear. It is possible that women with the highest level of education may be more likely to use alternative screening services e.g., privately funded screening not captured on the NHSCSP. Further, given that previous studies were limited in the range of personal factors included in their models, residual confounding may still be a problem in these studies and may account for some of the associations previously reported.

Behavioural factors

Higher odds of non-attendance for screening in women who had higher BMI and were current smokers, as reported in this chapter, have been previously documented in other organised screening programmes outside the NHSCSP.[158, 161] With regard to obesity, it has been suggested that these women are less likely to attend because of fear of embarrassment, fear of a lack of equipment for larger body sizes and unwanted lectures on weight loss.[170–172] Lower attendance at screening for current smokers may reflect a generally lower endorsement of behaviours that enhance health.[173] Similarly, it may be possible that current smokers may be less likely to attend in order to avoid behaviour change interventions delivered by GPs or other healthcare practitioners during routine consultations.[174, 175]

Reproductive factors

Nulliparous women have been reported to be more likely to not attend for organised cervical screening in other countries.[153, 156, 158–160] One possible explanation for this difference is that parous women would have been exposed to obstetric care which forms an avenue for counselling and scheduling of appointments. However, the results in this chapter were much more striking than those in previous reports, which may reflect unknown particularities of nulliparous women in the MWS cohort

and further investigation is warranted. Unmeasured explanatory factors such as sexual orientation may also be an important omission in this group of women.[176]

Higher odds of non-attendance with increasing multiparity have also been previously documented outside England.[158, 159], and may point to time constraints as an explanation for non-participation in women with multiple children.[177]

The associations reported in this chapter on age at first FTP are novel to the best of my knowledge and may be an indication of increased social disadvantage which has been shown to drive younger parenthood.[178] Although this study was able to adjust for SES and education, many of these socio-demographic variables which have been shown to affect attendance for screening e.g. lower SES, lower education, foreign-born status or home ownership, are highly correlated, with complex interactions and confounding which I may have not been able to account for.[178]

Hormonal factors

These results are also consistent with one previous study outside England showing higher odds of non-attendance in non-users of OCs.[160] Women attending clinics to receive prescriptions for OCs may receive counselling on the importance of screening and may schedule for appointments. The associations reported in this chapter on MHT have not been reported elsewhere to my knowledge but may be similarly explained.

4.3.4.3 Strengths and limitations

The major strength of this analysis is in the unique dataset i.e. the linkage of objective NHSCSP screening records and the MWS, a large cohort of well-characterised participants, which offers several advantages. First, as the MWS has collected detailed information on a wide range personal factors, including established risk factors for cervical cancer such as OC use, parity, age at first FTP and smoking, this study presents findings on associations between personal factors and screening attendance beyond sociodemographic factors for the first time in England. Second, the range of factors has also allowed for more robust adjustment for potential confounding than previous studies. Third, the linked screening records allow for

a more objective determination of screening attendance than in previous reports that mostly relied on self-report and therefore were subject to bias. Finally, this is the largest English investigation thus far reporting on factors influencing screening attendance as far as I am aware, with over 800,000 participants included (the previous largest study using NHSCSP records had 72,613 women).[142]

The study is not without limitations. First, information on screening invitations to the NHSCSP was not available in this study and therefore it is not possible to assess whether women who did not attend for screening declined invitations or did not have the opportunity to attend i.e. did not receive invitations. However performance audits are routinely performed on the NHSCSP, and based on reports during the screening history period of this investigation it is unlikely that women were not invited.[101, 179] Second, the definition of screening history used herein may be subject to some misclassification as women who were recruited in 1996 would only have an approx. 8 years interval. However, majority of women were recruited for the MWS post-1998 (approx. 350,000 women recruited 1996- June 1998[180]. Third, as information on personal factors was collected at the end of the study period i.e., during recruitment into the MWS, recorded characteristics may not have been consistent during the study period i.e. in the previous 10 years. Fourth, although the number of missing values for the exposures investigated in this chapter is generally low (<1%), there are a few variables in these analyses with a slightly higher proportion of missing values at baseline: BMI (5%), education (3%) and age at first FTP (3%). My results were not materially altered when restricted to women with complete information. However, it is possible that these values may not be missing completely at random.

Finally, it worth noting the study period for this study and participants included may not be directly comparable to current practices. The NHSCSP has undergone several changes since this study period (see **Chapter 2**). However, findings herein are likely to be relevant today for the following reasons: 1) the NHSCSP currently invites all women aged 25-64 (20-64 in our study period) and there is no evidence to suggest substantial differences in routine screening practice i.e., actual screening

procedure when a woman attends for an appointment; and 2) at time of recruitment, women in the MWS were from a wide range of socioeconomic backgrounds and behaviours which were broadly typical of older white U.K. women allowing data to address a wide range of questions over time.[129] These analyses were also based on older women aged 56 years at recruitment i.e. women who were aged 46 years at the start of the study period, and do not address factors influencing attendance in younger women within the eligible age range for screening. It is also worth noting that 96% of women were of white ethnicity in the MWS cohort, a figure higher than national census data showing 81% white ethnicity in England in 2021[181] but similar to 2001 figures (91% white). It is therefore expected that while the findings herein are likely to be representative of women in this age group at the time of recruitment (1996-2001), they may not be reflective of the current more ethnically diverse population.

4.4 Conclusions

In this largest study of factors influencing screening non-attendance in England to date, it has been shown that non-attenders and attenders for cervical screening differed considerably, not only by age and SES, as has been reported previously, but also by behavioural, reproductive and hormonal factors. This study has also shown for the first time that differences by personal factors also exist among attenders by time since last test. Nulliparity was the strongest predictor of both non-attendance and poor attendance.

4.5 Tables

Publication	Region (Population)	Age range, years	n	Screening history assessment	Non-attender definition	% Non-attenders	Odds of non-attendance OR (95% CI)								Adjustments
							Sociodemographic			Behavioural		Reproductive		Hormonal		
							Age	SES	Education	Smoking	BMI	Parity	Age at first FTP	OC use	MHT use	
Webb et al.,2004[142]	Manchester	30-64	72,613	NHSCSP records	No history of attendance for NHS screening services (% never attended)	10.7	1.66 (1.48-1.86) for ages 60-64 vs under 50 years	1.27 (1.11-1.45) for area Townsend most vs. least deprived quartile	—	—	—	—	—	—	—	**Individual level**:age, place of birth. **Area level**: deprivation, % single person households, % persons moved in last year **Practice level**: practice size, single handed status, ethnicity by gender, employment status
Sutton et al., 2005[143]	England, Wales and Scotland	20-64	1,307	Self-report	No Pap smear in last 5 years	8	1.61 (0.74-3.57) for ages 55-64 vs. 25.34 years	1.03 (0.47-2.22) for lowest income vs. middle income quintile; 1.92 (0.98-3.85) for highest income vs. middle income quintile [a]	0.40 (0.22-0.70) for age 19-25 vs 15-18 at completion of full time education; 0.56 (0.16-2.09) for age 25+ vs 15-18 at completion of full time education	—	—	—	—	—	—	Age, marital status, education. Attitude and belief variables
Marlow et al., 2008[144]	England, Wales and Scotland	25-64	994	Self-report	Never had a cervical cancer screening test	11	1.08 (0.67-1.85) for ages 55-64 vs. 25-34 years[a]	1.10 (0.64-1.85) for lowest vs. highest income tertile	1.82 (1.18-2.78) for no qualification vs. minimum qualifications (GCSE)	—	—	—	—	—	—	Marital status, education level and reading leaflets
Waller et al.,2009 [146]	England	26-64	580	Self-report	Never had a smear test or overdue for screening	15	1.44 (0.68- 3.13) for ages 55-64 vs. 26-34 years	—	0.75 (0.40-1.43) for ages 16 vs 19 or over at completion of education	—	—	—	—	—	—	Age, ethnicity, relationship status, age at completion of education
Moser et al.,2009[145]	England, Wales and Scotland	40-74	3,185	Self-report	Never had a cervical smear	9	—	1.51(1.03-2.20) for women in routine/manual (low income) vs. intermediate occupations (high income)	1.79 (1.01-3.13) for no qualification vs degree or equivalent	—	—	—	—	—	—	Age, cars, housing tenure, highest level of education, National Statistics socioeconomic classification, ethnic group, and region.
Marlow et al., 2015[147]	England (BAME backgrounds)	30-60	709	Self-report	No screen in last 5 years	53	1.95 (1.21–3.15) for ages 51-60 vs. 30-40 years	—	0.82 (0.41- 1.61) for no formal qualification vs. degree	—	—	—	—	—	—	Age, marital status, educational qualification, migration status, ability to read English
Marlow et al., 2017[148]	England, Wales and Scotland	25-64	3,111	Self-report	No Pap-smear,overdue Pap smear, or up-to date and no intention to attend in future	27	0.57 (0.44-0.72) for ages 55-64 vs 25-34 years	3.13 (2.33-4.34) for social grade E (lowest income) vs. AB (highest income)	—	—	—	—	—	—	—	—

Table 4.1: Studies published after 1988 on personal factors influencing non-attendance to the NHS Cervical Screening Programme

Abbreviations: n-Number, OR-odds ratio, CI-confidence interval, SES-socioeconomic status,
GCSE- General Certificate of Secondary Education, BMI-body mass index, OC- oral contraceptives, MHT -menopausal hormone therapy
[a] Result from model adjusted only for age

	% (n) of women*			
	Non-attender (n=24 338)	Attenders (n= 849 837)	Poor attenders (n=40845)	Good attenders (n=808 992)
Mean age at recruitment (SD)	57.2 (4.6)	56.1 (4.4)	56.8 (4.6)	56.1 (4.4)
Most deprived tertile	40 (9 812)	33 (277 024)	38 (15 518)	32 (261 506)
No educational qualification	4 (883)	2 (19 737)	3 (1 122)	2 (18 615)
Body mass index 30+kg/m^2	23 (5 159)	17 (135 437)	23 (8 802)	16 (126 635)
Current smokers	20 (4 826)	19 (162 576)	25 (10 174)	19 (152 402)
Nulliparous	48 (11 488)	10 (87 770)	19 (7 804)	10 (79 966)
Ever oral contraceptive use	31 (7 480)	61 (516 024)	52 (20 960)	62 (495 064)
Ever menopausal hormone therapy use	18 (4 194)	45 (374 776)	28 (11 440)	45 (363 336)
Among parous women:				
Mean number of FTPs (SD)	1.3 (1.5)	2.1 (1.2)	2 (1.5)	2.2 (1.2)
Age at first FTP <18 years	3 (396)	3 (20 349)	3 (992)	3 (19 357)

Table 4.2: Characteristics at recruitment, by recorded attendance at screening

Abbreviations: SD, standard deviation, FTP, full-term pregnancy
* unless otherwise indicated

	No. of non-attenders/attenders	OR for non-attendance vs. attendance		No. of poor/good attenders	OR for poor attendance vs. good attendance	
		Minimally adjusted±	Fully adjusted (95% CI)		Minimally adjusted±	Fully adjusted (95% CI)
Age at recruitment, years						
<55	9073/398 107	**1.00**	**1.00** (–)	16629/381 478	**1.00**	**1.00** (–)
55-60	6861/246 682	1.22	1.12 (1.09, 1.16)	11558/235 124	1.13	1.14 (1.11, 1.17)
60-64	8404/205 048	1.80	1.29 (1.25, 1.33)	12658/192 390	1.51	1.37 (1.34, 1.41)
		p<0.001	Het. χ^2_2=227.6 p<0.001		p<0.001	Het. χ^2_2 = 597.9 p<0.001
Deprivation tertile						
Least deprived,1	6480/286 407	**1.00**	**1.00** (–)	11918/274 489	**1.00**	**1.00** (–)
2	8046/286 406	1.22	1.17 (1.13, 1.21)	13409/272 997	1.11	1.07 (1.05, 1.10)
Most deprived, 3	9812/277 024	1.55	1.41 (1.37, 1.46)	15518/261 506	1.36	1.23 (1.19, 1.26)
		p<0.001	Het. χ^2_2= 405.3 p<0.001		p<0.001	Het. χ^2_2= 252.4 p<0.001
Educational qualifications						
None	9535/338 522	**1.00**	**1.00** (–)	16844/321 678	**1.00**	**1.00** (–)
Technical	3487/132 986	0.92	1.02 (0.99, 1.07)	6058/126 928	0.91	1.03 (1.00, 1.06)
Secondary	5729/224 334	0.91	1.07 (1.03, 1.11)	10227/214 107	0.92	1.08 (1.05, 1.11)
Tertiary	3848/112 240	1.24	1.29 (1.24, 1.35)	5307/106 933	0.97	1.13 (1.09, 1.17)
		p<0001	Het. χ^2_3=139.7 p<0.001		p<0.001	Het. χ^2_3=59.1 p<0.001

Table 4.3: Odds ratios (95% CI) for non-attendance versus attendance and poor versus good attendance i.e., attendance >5 years versus attendance ≤5 years before recruitment for organised cervical screening according to socio-demographic factors

Abbreviations: OR, odds ratio; CI, confidence interval
±Minimally adjusted models were adjusted for age at recruitment and region of residence
Fully adjusted models were additionally adjusted for deprivation tertiles, educational qualifications, body mass index, smoking status, oral contraceptive use, menopausal hormone therapy and parity where appropriate.
All p-values represent p-value for heterogeneity

	No. of non-attenders/attenders	OR for non-attendance vs. attendance		No. of poor/good attenders	OR for poor attendance vs. good attendance	
		Minimally adjusted±	Fully adjusted (95% CI)		Minimally adjusted±	Fully adjusted (95% CI)
Body mass index, kg/m²						
<25	9753/391 710	**1.00**	**1.00** (–)	16085/375 625	**1.00**	**1.00** (–)
25-29	7432/279 480	1.05	1.10 (1.07, 1.14)	13105/266 375	1.13	1.16 (1.13, 1.18)
30+	5159/135 437	1.51	1.46 (1.41, 1.52)	8802/126 335	1.61	1.59 (1.55, 1.64)
		p<0.001	Het. χ^2_2= 411.3 p<0.001		p<0.001	Het. χ^2_2= 1053.7 p<0.001
Smoking status						
Never	12858/411 981	**1.00**	**1.00** (–)	18778/393 203	**1.00**	**1.00** (–)
Past	6401/269 016	0.77	0.85 (0.82, 0.88)	11560/257456	0.94	0.97 (0.95, 1.00)
Current	4826/162 576	1.00	1.18 (1.14, 1.22)	10174/152 402	1.45	1.55 (1.51 1.59)
		p<0.001	Het. χ^2_2= 261.9 p<0.001		p<0.001	Het. χ^2_2=1263.2 p<0.001

Table 4.4: Odds ratios (95% CI) for non-attendance versus attendance and poor versus good attendance i.e., attendance >5 years versus attendance ≤5 years before recruitment for organised cervical screening according to behavioural factors

Abbreviations: OR, odds ratio; CI, confidence interval
±Minimally adjusted models were adjusted for age at recruitment, region of residence.
Fully adjusted models were additionally adjusted for deprivation tertiles, educational qualifications, body mass index, smoking status, oral contraceptive use, menopausal hormone therapy, parity where appropriate.
All p-values represent p-value for heterogeneity.

	No. of non-attenders/attenders	OR for non-attendance vs. attendance		No. of poor/good attenders	OR for poor attendance vs. good attendance	
		Minimally adjusted±	Fully adjusted (95% CI)		Minimally adjusted±	Fully adjusted (95% CI)
Parity±						
Parous	12636/758852	**1.00**	**1.00** (–)	32842/726010	**1.00**	**1.00** (–)
Nulliparous	11488/87770	7.87	7.02 (6.84, 7.22)	7804/79966	2.16	2.15 (2.10, 2.21)
		p<0.001	Het. χ^2_1= 17503.9 p<0.001)		p<0.001	Het. χ^2_1= 2866.6 p<0.001
Among parous women:						
Number of FTPs						
1-2	90985/483 465	**1.00**	**1.00** (–)	82982/463 842	**1.00**	**1.00** (–)
3-4	7636/246 105	1.03	0.98 (0.94, 1.01)	19623/234 871	1.10	1.06 (1.04, 1.09)
5+	4174/29282	1.61	1.22 (1.13, 1.32)	11234/27297	1.62	1.35 (1.28, 1.42)
		p<0.001	Het. χ^2_2= 30.1 p<0.001		p<0.001	Het. χ^2_2= 129.3 p<0.001
Age at first FTP, years						
<18	396/20296	1.30	1.17 (1.05, 1.30)	992/19357	1.23	1.07 (1.00, 1.15)
18-20	2190/129 661	1.08	1.04 (0.98, 1.09)	5864/123 797	1.11	1.03 (0.99, 1.06)
21-24	4634/286 154	**1.00**	**1.00** (–)	11995/274 159	**1.00**	**1.00** (–)
25+	4968/303 013	1.01	1.03 (0.99, 1.07)	12877/290 136	1.01	1.07 (0.99, 1.10)
		p<0.001	Het. χ^2_3=9.1 p=0.02		p<0.001	Het. χ^2_3=15.2 p=0.001

Table 4.5: Odds ratios (95% CI) for non-attendance versus attendance and poor versus good attendance i.e., attendance >5 years versus attendance ≤5 years before recruitment for organised cervical screening according to reproductive factors

Abbreviations: OR, odds ratio; CI, confidence interval; FTPs, full-term pregnancies
±Minimally adjusted models were adjusted for age at recruitment, region of residence.
Fully adjusted models were additionally adjusted for deprivation tertiles, educational qualifications, body mass index, smoking status, oral contraceptive use, menopausal hormone therapy. Models in parous women only were also adjusted for number of FTPs or age at first FTP as appropriate.
All p-values represent p-value for heterogeneity.

	No. of non-attenders/attenders	OR for non-attendance vs. attendance		No. of poor/good attenders	OR for poor attendance vs. good attendance	
		Minimally adjusted±	Fully adjusted (95% CI)		Minimally adjusted±	Fully adjusted (95% CI)
Oral contraceptive use						
Never	16355/325 961	**1.00**	**1.00** (–)	19357/305 604	**1.00**	**1.00** (–)
Ever	7480/516 024	0.30	0.43 (0.41, 0.44)	20960/495064	0.72	0.82 (0.80, 0.84)
		p<0.001	Het. χ^2_1= 3208.8 p<0.001		p<0.001	Het. χ^2_1 330.3 p<0.001
Menopausal hormone therapy use						
Never	19699/465 724	**1.00**	**1.00** (–)	28862/436 862	**1.00**	**1.00** (–)
Ever	4194/374 776	0.27	0.31 (0.30, 0.32)	11440/363 336	0.48	0.50 (0.49, 0.51)
		p<0.001	Het. χ^2_1= 5349.5 p<0.001		p<0.001	Het. χ^2_1= 3988.3 p<0.001

Table 4.6: Odds ratios (95% CI) for non-attendance versus attendance and poor versus good attendance i.e., attendance >5 years versus attendance ≤5 years before recruitment for organised cervical screening according to hormonal factors

Abbreviations: OR, odds ratio; CI, confidence interval; FTPs, full-term pregnancies
±Minimally adjusted models were adjusted for age at recruitment, region of residence.
Fully adjusted models were additionally adjusted for deprivation tertiles, educational qualifications, body mass index, smoking status, oral contraceptive use, menopausal hormone therapy, parity where appropriate.
All p-values represent p-value for heterogeneity.

"What is it saying?," she asked
"One day you'll know. Today just listen."

— Yvonne Adhiambo Owuor

5

Screening history and the risk of cervical neoplasia

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5.1 Introduction

The broad objective of this thesis is to use data from the Million Women Study (MWS) to examine the association of reproductive and hormonal factors and the risk of cervical neoplasia i.e., cervical intraepithelial neoplasia grade 3 (CIN3) and invasive cervical cancer (ICC), after adjusting for potential confounding by screening history. The analyses presented in **Chapter 4** have shown that attendance for screening is associated with both reproductive and hormonal factors. This chapter now explores the relationship between screening history, in terms of previous attendance and previous test results prior to recruitment into the MWS, and the subsequent risk of cervical neoplasia.

Prior to 2003, and hence prior to recruitment into the MWS, the NHS Cervical Screening Programme (NHSCSP) used conventional cytology tests ("Pap smears") as a primary cervical screening test. The International Agency for Research on Cancer (IARC) has recently concluded that a history of attendance for screening by Pap smear is causally associated with a reduction in the risk of ICC where appropriate follow-up and treatment is available.[16] However, there is evidence that the association between screening attendance and ICC varies between the two major histo-types, with a more modest association found for adenocarcinoma (AC) than for squamous cell carcinoma (SCC).[8] High-grade precursor lesions including CIN3 are detected at screening and the incidence (detection rates) of CIN3 is therefore widely accepted to be related to attending for Pap-smear based screening.[15, 93, 182] Much less is known about potential associations between previous Pap smear test results and the risk of subsequent cervical neoplasia, although some studies have indicated a persistently increased risk of CIN3 and ICC in women with previous abnormalities.[183–186]

In this chapter, I present the findings of a narrative review of previous evidence on screening history and the incidence of cervical neoplasia i.e., CIN3 and overall ICC, including separately by major histo-type, SCC and AC. I then report on an investigation of these relationships in the large MWS cohort with linked

individual screening records from the NHSCSP and almost two decades of follow-up. Specifically, this study 1) evaluates the association between previous screening attendance and risk of CIN3 and ICC overall; 2) evaluates the association between previous screening test results and risk of CIN3 and ICC overall; 3) evaluates the association between screening history and risk of CIN3 and ICC overall; and 4) examines the relationship between previous screening attendance, previous screening test results, and screening history in relation to ICC risk by histological tumour type, SCC and AC.

5.2 Literature Review

5.2.1 Objectives

The aim of this review is to summarise previous evidence on the the risk of cervical neoplasia i.e., CIN3 and ICC including separately by major histo-type SCC and AC, associated with previous screening history, defined as previous attendance and previous cervical cytology test results (referred to as “previous abnormalities").

5.2.2 Methods

To summarise what is known on the risk of cervical neoplasia and conventional cytological screening history as defined, I first present a summary of three systematic reviews that report on the association between previous attendance for cervical screening and the risk of ICC. The first review published by IARC as part of their 2005 *Handbook of Cancer Prevention* aimed to provide an evaluation of the effect of various cervical screening tests, including conventional cytology, on the incidence of overall ICC.[187] The second review, a 2013 publication by Peirson *et al.* had a broadly similar aim to IARC, but was conducted to inform Canadian screening policy and examined the literature from 1995 to the more recent date of April 2012.[188]. These two reviews contain the majority of the evidence underlying the recent IARC evaluation of screening as causally preventive of ICC.[16] The final review, authored by the International Collaboration of Epidemiological Studies of Cervical Cancers (“the Collaboration”) in 2007 and underlying current perspectives by histo-type, was an individual-participant data meta-analysis of all observational evidence comparing a history of attendance for screening between SCC and AC.[8]

I then present the findings of a literature search of online database PubMed for: 1) subsequently published evidence on screening attendance in relation to overall ICC [May 2012 to 1 May 2022] and separately by histo-type [March 2007 to 1 May 2022]; 2) all available evidence on screening attendance in relation to CIN3; and 3) all available evidence on previous abnormalities in relation to all cervical neoplasia to 1 May 2022. Search strategy is detailed in **Table 5.1**. Results were reviewed for

relevance based on titles/abstracts and all identified papers extracted to Mendeley bibliographic database for full text review. Additional papers were identified by searching reference lists of identified full-text papers.

Only studies that were based on cohort or case-control studies with comparison groups and which were published as full papers in peer-reviewed journals were included. Only articles reporting associations between the risk of cervical neoplasia and cervical screening history (previous attendance or abnormality or both) by conventional “Pap-smear" cytology occurring within organised screening programmes only were included. Studies reporting on other screening methods or opportunistic screening were excluded. Studies on rare types of ICC were excluded. All articles reporting relative risks (RR) and confidence intervals (CI), with adjustment at least for age, for the incidence of CIN3, overall ICC, and/or the two major histo-types of ICC, SCC or AC were included.

5.2.3 Results

Since the two reviews,[187, 188] three studies have been published on the risk of overall ICC in relation to attendance for screening[184, 186, 189] with two more studies stratified by histo-type [185, 190]. I found no cohort or case-control evidence on the risk of CIN3 associated with attendance for screening.

A total of five studies have reported on relationships with previous abnormality: four reporting on overall ICC,[183–186], two studies on SCC and AC,[185, 189] and one on CIN3.[183]

Study characteristics and results of all studies, including the review papers, are presented in **Tables 5.2-5.6** and in text.

5.2.3.1 Attendance for screening

As mentioned, on the basis of all previous evidence to October 2020, IARC has recently concluded that a causal preventive association between the use of cervical cytological screening and incidence of ICC is established.[16] Majority of this evidence was included in the two systematic reviews, as well as subsequently

published evidence, summarised here and in **Tables 5.2 and 5.3** respectively. I found no cohort or case-control evidence on the risk of CIN3 associated with attendance for screening, and the following section relates to the risk of ICC only.

Systematic reviews and meta-analyses

The first review, the IARC study,[187] was based on the early observational studies originally set up to evaluate the efficacy of screening and the relatively few (6) cohort studies came from countries where screening programmes were first established— Canada, Finland, Iceland, Norway, Denmark and Sweden, spanning the late 1960s-1990s.[90, 191–195] Exposure was screening attendance defined as either invitation to screening[195] or as participation in screening[90, 191–194] against an outcome of incident ICC. Incidence rates expected in the absence of screening i.e, reference rates, were calculated from general population rates during the period before screening or population rates in areas without a screening programme in most studies.[90, 191, 192, 194] Later studies used reference rates from non-participants and relative risks (RR) were calculated by comparing ever and never screened women,[193] or from the average rates in the general population during the screening period.[194] A significant reduction in the incidence of ICC was observed among screened women in all studies, but with large variation in effect with risk estimates ranging from RR 0.16, 95% CI: 0.09-0.29 in British Columbia, Canada [191] to 0.62, 95% CI: 0.52-0.75 in Norway[192] for observed vs. expected incidence among screened women(see **Table 5.2**). Seventeen case-control studies on incidence were identified by the IARC Working Group.[196–212] Exposure was defined as the screening attendance status, not by screening invitation in the studies. However, studies had widely different approaches with respect to screening setting (organised vs opportunistic); eligibility of controls (hospital vs. population-based); assessment of screening history (definition of screening tests vs. “diagnostic" tests); outcome (stage of cervical cancer vs. analyses by histo-type); and variable adjustment for potential confounding. Nonetheless, OR estimates were fairly similar and a pooled OR estimate of 0.34, 95% CI: 0.31-0.38 for ever vs never screened women was

calculated, (**Table 5.2**) although the IARC Working Group noted that this estimate should be interpreted with caution due to limitations of the individual studies.[187]

Pierson *et al.,* identified a total of 14 studies: an RCT,[213] a cohort study[214] and a dozen case-control studies,[185, 203, 207–209, 212, 215–220] including five studies previously included by IARC. The RCT included is the first ever published trial on the efficacy of Pap smear screening compared to a control group, to my knowledge.[213] This cluster-randomised trial, conducted in a largely unscreened population in India, compared women receiving a single round of screening by cytology to control women receiving health education on the symptoms of cervical cancer and the availability of screening. After an average follow-up of 8 years, there were no significant associations observed between the test and control arms both for the incidence of overall ICC and advanced ICC (International Federation of Gynaecology and Obstetrics Stage [FIGO] II+) with estimated risks as follows: HR: 1.34, 95% CI: 0.99-1.8, 152 vs 118 cases for overall ICC and HR: 0.75, 95% CI: 0.51-1.10, 58 vs 82 cases for advanced ICC.[213] (see **Table 5.2**) The cohort study, published by Herbert *et al.* in 1996, studied the incidence of ICC in the Southampton and South West Hampshire region of the U.K after the introduction of the NHSCSP and primarily aimed to provide guidance on screening intervals.[214] Because of this aim and the short-term follow-up of this cohort, it was not included by the IARC Working Group in their evaluation on efficacy of screening.[187] In the cohort of 116,022 women, the incidence of ICC was 62% lower in women who had been screened in the previous five years than in those who had not (RR 0.38, 95% CI: 0.23-0.63). Finally, in a meta-analysis of almost 4800 cases and 18 000 controls from the dozen studies, Peirson *et al.,* found lower odds of having attended for screening in women who were diagnosed with ICC, although a large degree of heterogeneity was noted (OR 0.35, 95% CI= 0.30-0.41, heterogeneity: $p<0.00001$). Attendance for screening in the pooled analyses ranged from within the previous 3 years to a single lifetime screen.(see **Table 5.2**)

To my knowledge, three studies have been published on the association between attendance for screening in organised programmes and ICC since the two reviews

(after May 2012).[184, 186, 221] (see **Table 5.3**) The first, a Swedish cohort study of 569,132 women followed for a median of 11 years, focused on older women and examined their screening history at age 51-60 to assess the impact of screening at age 61-65 on the risk of ICC at ages 61-80 years. A total of 868 cases of ICC were diagnosed and after adjusting for birth cohort and education, they found that the risk reduction associated with screening at age 61-65 relative to not screening at that age was greatest for women who were unscreened at ages 51-60 (RR: 0.42, 95%CI: 0.24-0.72 for screened vs unscreened at age 61-65, in women unscreened at age 51-60 years). [221] The other two studies were population based-case control studies which, despite differences in study population, reported fairly similar results.[184, 186] The first study was based on an audit of the Swedish cervical screening programme during the period between 2002-2011, published in 2020.[184] During this period, the programme invited women aged 23-65 years at intervals of 3 or 5 years dependent on age. From just over 4,000 cases with 30 population-based controls per case, they found that eligible women who had had two tests in two screening rounds had 76% lower odds of developing ICC compared to women who were not screened at all in two rounds of screening (OR: 0.24, 95% CI: 0.22-0.26).[184] Results from the U.K. showed that for older women exiting the NHSCSP, screening at least every 5.5 years between ages 50-64 years was associated with 75% lower odds of ICC after age 65 (OR: 0.25, 95% CI: 0.21-0.30) based on 1341 cases and 2646 age-matched controls.[186]

5.2.3.2 Previous abnormalities

A note on terminology

As discussed in **Chapter 2**, there are several different systems for classifying cervical abnormalities, derived from the original Papanicolaou system. [102] These are compared in **Table 2.2, Chapter 2**. In the U.K., the British Society for Clinical Cytology (BSCC) system is used where the more common squamous precursor lesions are broadly divided into borderline nuclear change and mild, moderate or severe dyskaryosis.[102] Adenocarcinoma precursor lesions are classified in the

BSCC system as either borderline nuclear change or "?"[query/suspected] glandular neoplasia. The BSCC system is also used in the analysis section of this chapter. However, several of the studies reporting on previous abnormalities included in this review,[183–185] make use of the Bethesda classification system.[102] According to the Bethesda system: squamous precursor lesions showing BSCC borderline nuclear change are classified as atypical squamous cells of unknown significance (ASCUS); lesions showing mild dyskaryosis are classified as low-grade squamous intraepithelial lesions (LSIL); and lesions showing moderate or severe dyskaryosis are classified as high-grade squamous intraepithelial lesions (HSIL). The Bethesda system classifies adenocarcinoma lesions as either atypical glandular cells [AGC] (corresponding to BSCC borderline nuclear change) or adenocarcinoma *in situ* (corresponding to BSCC severe dyskaryosis or "?"[query/suspected] glandular neoplasia).

Invasive cervical cancer

To my knowledge, four published studies (one cohort, three case-control) have reported on the association between previous abnormalities and the subsequent risk of ICC among attenders of an organised screening programme.[183–186, 221] (see **Table 5.4**)

The first, a Norwegian cohort study designed to evaluate follow-up procedures for women with abnormal tests, compared the risk of ICC in women with normal tests versus those with ASCUS tests.[183] Generally, Norwegian screening protocols recommend that women aged 25–69 years have a Pap test every 3 years and women with normal tests are returned to routine recall. Those with low-grade abnormalities, like ASCUS, are recalled for an earlier repeat test within 6 months, and women who have normal repeat smears are returned to routine recall.[222] In this study, a cohort of 536,398 women with normal and ASCUS index tests were followed for the incidence of a cytological lesion or outcome (ICC) after 2 years in the first instance (short-term follow up) and then again after 7 years (long-term follow-up). A total of 231 cases of ICC were diagnosed in this cohort. Among 6,462 women with an ASCUS index test with repeat normal tests after short-term follow-up (who would

have been returned to routine screening recall), the risk of ICC remained elevated at more than three-fold that of women who had had normal index tests, but no known further tests (RR: 3.9, 95% CI: 2.1-7.2).[183] These analyses were, however, based on only 21 cases diagnosed at various times during follow-up.

Of the three case-control studies, two presented the findings of a nationwide audit of the Swedish cervical cancer screening programme: one in 1999-2001[185] and another 2002-2011[184] Screening guidelines were similar in both periods of audit and a woman was considered to have had an abnormal test if at least one test taken within the recommended interval (3 or 5 years) was an ASCUS, LSIL or HSIL result, or a test classified as “not satisfactory for evaluation" without a subsequent normal test. They found that the odds of ICC were higher for women with abnormal tests compared to women with normal tests taken within the same period (OR: 7.55, 95% CI: 5.88-9.69 for abnormal (141 cases) vs normal tests (300 cases) within 6.5 years, [185] and OR: 17.4, 95% CI: 13.3-22.8 for abnormal (72 cases) vs normal tests (651 cases) in 2 rounds [184]). The results from the final study, the previously mentioned U.K based case-control study on older women were based on a total of 341 cases and 2646 age-matched controls.[186] They found an increase in the odds of ICC of more than ten-fold after 65 years for women who had had abnormal tests at ages 50-64 years compared to those with normal tests in the same period(OR: 11.52, 95% CI: 8.57-15.47). In this case, women were classified as having abnormal tests if they had low-grade abnormality (ASCUS or LSIL) at age 50–64 years that was not followed by three consecutive negatives or HSIL cytology regardless of whether or not it was followed by three consecutive negatives.

CIN3

To my knowledge, there are no published studies reporting results on the association between previous abnormalities and the risk of CIN3 as a single outcome. However, the same Norwegian cohort study evaluating follow-up procedures for women with ASCUS tests,[183] reported on the risk of CIN2/3 (a composite outcome) associated with previous abnormalities. (see **Table 5.4**) Based on 365 cases of CIN2/3, they

again found that for women with an ASCUS index test and repeat normal tests after short-term follow-up (2 years), the risk of CIN2/3 after longer follow-up (7 years) was elevated compared to women who had had normal index tests, but no further tests (RR: 3.6, 95% CI: 3.1-4.3).

5.2.3.3 Histological subtype

Attendance for screening

Systematic review and meta-analysis

The Collaboration included a total of 8097 women with SCC, 1374 women with AC (of which 26% were adenosquamous carcinoma) and 26,445 controls. They found that a history of attendance for a Pap smear was associated with a considerable reduction in risk of SCC (RR: 0.46, 95% CI: 0.42–0.50) and with a significant but smaller reduction in risk of AC (RR: 0.68, 95% CI: 0.56–0.82) as presented in **Table 5.5**. The difference between the two types was also found to be statistically significant (heterogeneity: p=0.002).[8]

Subsequently, two published studies[185, 190] have reported on attendance for screening and the risk of ICC stratified by histo-types presented in **Table 5.5**. Based on a total of 12,418 cases with ICC in the U.K. (75% SCC and 22% AC) and 24,453 age-matched controls, it was reported that women who were up to date with screening i.e., attended screening in the last 3.5 or 5.5 years depending on age, had lower odds of both SCC and AC compared to never screened women i.e., women who had no record of attendance for screening. However, the reduction in odds appeared to be significantly greater for SCC than for AC (ORs: 0.14, 95% CI: 0.12-0.15 and 0.46, 95% CI: 0.39-0.55 for SCC and AC respectively).[190] (see **Table 5.5**) Similarly, in Sweden,[185] based on 921 squamous and 309 non-squamous cancers (79% AC) with 6,124 age-matched controls, the reduction in odds appeared to be larger for squamous than non-squamous for women attending within the recommended screening interval i.e., 0.5-5.5 years before index/diagnosis date, compared to those who had not (OR: 0.33, 95% CI: 0.29-0.40 and 0.63, 95% CI:

0.47-0.83). No tests for heterogeneity were reported in either of studies, although CIs do not overlap suggesting a statistically significant difference.

Abnormalities at previous screen

The evidence on the risk of ICC by histo-type associated with previous abnormalities within an organised programme is extremely limited. To my knowledge, only two studies (one cohort[189] and one case-control[185]) have been published reporting on the risk of SCC and AC associated with previous abnormalities detected at screening.

The first was a Swedish cohort study which primarily aimed to investigate the risk of ICC, including stratified by histo-type, after the detection of atypical glandular cells (AGC) in all women resident in Sweden with a cytologic record between 1980-2011.[189] A woman was classified as having abnormalities if her first cytology record in the study period was AGC, LSIL or HSIL. Women with cytologically normal first tests recorded contributed to the cytologically normal risk time as long as they were screened i.e., had a test within 5 years of each normal result, and had only normal test results. From a total 187 and 48 cases of SCC and AC, women with previous abnormalities were shown to be at higher risk for both SCC and ACC, with the largest magnitude of increased risk for each cancer corresponding to its precursor abnormality. After 10.5-15.5 years of follow-up, compared to women with normal tests, the risk of SCC was highest in women with previous HSIL, LSIL and AGC in that order versus normal tests (IRRs [95% CI]: 6.7 [5.1-8.9]; 5.1 [4.3-6.1]; and 2.5 [0.7-6.7] for HSIL, LSIL and AGC respectively). Conversely, the risk of AC was highest in women with previous AGC, followed by women with LSIL and HSIL lesions respectively (IRRs [95% CI]: 9.4 [4.5-19.9]; 2.6 [1.8-3.8] and 3.3 [1.8-6.1]for AGC, LSIL and HSIL respectively)

The second study reporting results on previous abnormalities was the Swedish audit of 1999-2011[185] which included 921 squamous and 309 non-squamous cancers (79% AC) with 6124 age-matched controls. Again, a woman was considered to have an abnormal test if a test was taken within the recommended interval and at least one test had ASCUS, a LSIL or HSIL result, or was classified as “not

satisfactory for evaluation" without a subsequent normal test. They found that among women attending for screening within the recommended interval (0.5-5.5 years), those those who had abnormal Pap tests had a higher risk than those whose tests were normal for both squamous and non-squamous (ORs: 8.34, 95% CI: 6.14-11.32 and 6.07, 95% CI: 3.88-9.41 respectively).

Neither study reported formal tests for heterogeneity comparing the two histotypes, although overlapping CIs suggest no statistically significant differences between the two. (see **Table 5.6**)

5.2.4 Discussion

5.2.4.1 Attendance

Randomised trials are the most reliable way to evaluate changes in incidence following exposure to screening.[223] However, due to concerns on the ethics of withholding screening in control groups, only one RCT with control conditions on Pap-smear screening and the risk of ICC has ever been published.[213] As this study was conducted in India where there is little screening, women in the control group who only received counselling on symptoms, were considered to have received standard care. Contrary to previous evidence, the trial showed no significant associations in the risk of both overall ICC and advanced ICC (FIGO Stage II+) in women receiving a single round of Pap-screening vs. unscreened women. However, the minimal impact of screening seen in this study may be explained by increased screening activity in controls after health awareness and the low sensitivity of a single Pap smear test.[224] Further this study may have been relatively under-powered to detect a difference and had a relatively short follow-up time.

Evidence from observational studies has, however, consistently shown strong significant associations between the risk of ICC and screening history, although several biases are assumed in this body of evidence. Most of the observational evidence, including that in systematic reviews and meta-analyses, comes from case-control studies[184, 186–188] and is therefore at risk of biases associated with these studies in the evaluation of screening. First, studies must select controls whose

exposure experience is reflective of that of cases which may be difficult, for example, where hospital controls are used who may have higher screening activity than cases and potentially lower underlying risk.[196, 199, 203, 208–210, 212] Second, results may be underestimated if tests included in analysis are not only true screening tests but diagnostic tests. However, this can be difficult to decide retrospectively, particularly in studies which were conducted outside of an organised programme (included in previous reviews).[196, 199, 200, 203, 204, 208, 210, 212] Third, available case–control studies are a mixture of studies using administrative databases which cannot obtain detailed information to adjust for relevant confounding,[184, 186, 201, 202, 204, 205, 211] and studies using interviews or questionnaires which may be subject to participation and recall biases.[200, 203, 210, 212] Few cohort studies have evaluated the effect of cervical cancer screening on the subsequent risk of ICC. Although these studies are generally more reliable than the case-control studies, they have been limited by small numbers[90, 191, 194, 195] and the potential for bias in the later studies due to selected reference groups. For example, in the Swedish study included in the IARC review which compared participants to non-participants there may have been potential for selection of a more healthy group to participate.[193]

The evidence from the numerous observational studies, however, is compatible with the conclusion of a strong association between attendance for screening and ICC, that is consistent regardless of the different approaches with respect to screening settings, study populations, reference groups and exposure definitions. This evidence is also supported by ecological trend data in cervical cancer incidence in multiple countries which have shown a decline in the incidence of ICC after the introduction or expansion of screening.[83–87, 91–93, 225, 226] (see **Chapter 2 Section 2.4.2**) On the basis of these results, it is likely that only part of the variation seen in the observational studies is as a result of biases, and, in a recent evaluation, IARC has concluded that screening with conventional cytology or “Pap-smears" reduces the incidence of cervical cancer based on the weight of the evidence evaluated.[16] Although not investigated in observational studies, it is also widely accepted based

on time-trend data that cervical cytological screening is associated with an increased incidence of CIN3 which is only detected via screening.[14, 15, 85, 182, 227, 228]

5.2.4.2 Abnormalities

Epidemiological evaluation of the efficacy of screening has primarily focused on comparing risks between screened and unscreened women. It is taken that women who are screened, and have abnormal smears should receive appropriate follow-up and treatment to prevent progression of high-grade precursor lesions like CIN3 to invasion i.e., invasive cervical cancer; indeed, this is the key procedure that enables cervical screening to prevent cancer. However, the limited evidence examining this relationship all showed an elevated persistent risk of CIN2/3 and ICC in women with previous abnormalities, including low-grade abnormalities, compared to those with normal tests within organised programmes.[183–186]

5.2.4.3 Histological subtypes

Similar to the Collaboration's 2007 meta-analysis,[8] subsequently published studies also suggest that while attendance for screening is associated with a lower risk of both SCC and AC compared to non-attendance, associations with AC may be more modest.[98, 185, 190] With respect to previous abnormalities, similar to overall ICC, previous abnormalities were also associated with an increased risk of both SCC and AC compared to normal tests, among women attending for screening within an organised programme.[185, 189] However, there was little evidence of variation in the risk associated with previous abnormalities between histo-types, although no formal tests for heterogeneity have been conducted.

5.2.5 Conclusions

The aggregate of the evidence from previous studies emphasises the consistent and strong association between previous attendance for screening and ICC. This association has also been shown to vary by histo-type, with a stronger association for SCC than AC. Few studies have explored associations with previous test results, but the literature is suggestive of a strong association between previous abnormalities and cervical neoplasia i.e. CIN3 and ICC, and further investigation of this association is warranted. This association has also not been formally tested between histo-types, SCC and AC, and these analyses should be explored.

5.3 Screening history and the risk of cervical neoplasia

5.3.1 Objectives

The analysis that follows will examine the risk of CIN3 and ICC in relation to screening history, in terms of previous attendance and previous abnormalities, and explores potential variation in these associations by histological tumour type, SCC and AC.

5.3.2 Methods

5.3.2.1 Study cohort

Data were obtained from the Million Women Study (MWS) with linked NHSCSP records. The methods of recruitment, data collection, follow-up, and ascertainment of cervical cancer for the MWS; and extraction and linkage with routinely recorded NHSCSP screening data have been described in detail in **Chapter 3**.

After exclusions, (see **Chapter 3, Section 3.6.1**) total of 874,175 women were eligible for inclusion for the analyses of the risk of ICC and 843,389 for the risk of CIN3.

5.3.2.2 Exposures

Analyses examined three screening history variables assessed from NHSCSP records during the screening period for this thesis i.e., the period between the start of the NHSCSP (1st April 1988) and recruitment into the MWS (1996-2001).

First, analyses examined screening history categorised according to time since last test as a proxy for frequency of attendance. The definition of this variable has been described previously in **Chapter 4, Section 4.3.2.3**. Women who were classified as attenders in this thesis i.e., who had at least one test record during the screening history period, were further classified based on the time since their last test within the screening history period: $\leq$ 5years before recruitment, >5years before recruitment.

Second, analyses examined screening history categorised according to previous abnormalities ("no abnormality", "minor abnormalities", "major abnormalities") based on worst cytologic test result recorded during the entire screening history period. A woman was classified as having "no abnormality", if all her tests were negative, or as having "any abnormality", where any abnormalities were detected i.e., any dyskaryosis. A woman with any abnormality was classified as having "minor abnormalities" if her worst cytology was borderline nuclear change or mild dyskaryosis; and as having "major abnormalities" if her worst cytology was moderate or worse dyskaryosis. Additionally, a woman was classified as having a major abnormality if she had a CIN3 registration (10th International Classification of Diseases (ICD)-10 code D06) during the screening history period. Women with *only* inadequate tests who were referred to colposcopy were classified as having "minor abnormalities." This is because test results recorded as "inadequate" should have resulted in repeat testing within 6 months and referral to colposcopy after a third consecutive inadequate test.[162] (see **Figure 2.6, Chapter 2**)

Finally analyses examined screening history jointly i.e., previous abnormalities within categories of time since last test, due to the strong inter-relationship between the two where only women who attend for screening will have abnormalities detected. In this case, women in each category of attendance i.e., $\leq$ 5years before recruitment or >5years before recruitment were further classified according to previous abnormality during the entire screening history period. For this analysis, due to limited case numbers, previous abnormalities were examined as either "no abnormality" or "any abnormality." Categories for this analysis were: "$\leq$ 5 years before recruitment, no abnormality"; "$\leq$ 5 years before recruitment, any abnormality"; "$>$ 5 years before recruitment, no abnormality"; "$>$ 5 years before recruitment, any abnormality."

All three variables included a "no test record" category. Women were assigned this category if they had no tests recorded during the screening history period or if they had *only* inadequate tests. (see **Chapter 4, Section 4.3.2.3**) As the recommended screening interval for women during the screening history period

was 3 or 5 years, women with last test taken $\leq$ 5 years before recruitment will be referred to here as "good attenders", and those with last test taken >5 years before recruitment will be referred to as "poor attenders". The definition of the joint screening variable is presented in **Figure 5.1**

5.3.2.3 Outcomes

The main outcomes of interest were cervical intraepithelial neoplasia, grade 3 [CIN3] (ICD-10 D06) and invasive cervical cancer (ICD-10 C53). For analyses of histotype, the outcome was split into the two most common histological groups: SCC and AC by combining ICD-10 codes with ICD for Oncology, 3rd Edition morphology codes. For details on ascertainment of outcomes, please refer to **Chapter 3 Section 3.5**

5.3.2.4 Statistical analyses

Women contributed person-years from the date of recruitment until the earliest of the date of invasive cancer registration (excluding non-melanoma skin cancer, ICD-10 code C44), date of death or loss to follow-up, or the last date of follow-up (31 December 2018). For analysis of risk of CIN3, follow-up was additionally censored at a woman's 65th birthday as she would no longer be eligible for routine screening on the NHSCSP and screening history beyond recruitment into the MWS was not considered in these analyses. Cox proportional hazard regression models, with time in study as the underlying time variable, were used to calculate hazard ratios (referred to as relative risks [RRs]) and corresponding 95% confidence intervals (CIs) for CIN3/ICC in relation to screening history. Tests of heterogeneity in the relationship between ICC and screening history by histo-type i.e. SCC and AC were performed using a competing risks approach as described by Lunn and McNeil.[19] (see **Chapter 3 Section 3.6)**

All analyses were stratified by year of birth and year of recruitment, minimally adjusted for region of recruitment and socioeconomic status and additionally fully adjusted for education, smoking status, body mass index, parity and age at first birth, oral contraceptive [OC] use and use of menopausal hormone therapy [MHT]. For details on coding of adjustment variables, please refer to **Chapter 3 Section 3.6.2**

To examine the potential of mis-classification of screening according to time since last test in the choice of a 5-year screening window, a sensitivity analysis was conducted considering a 3-year window as invitation intervals were varied across Health Authorities (3 or 5 yearly) during the screening history period.[133]

5.3.3 Results

5.3.3.1 Study participants

Of 874,175 women, 24 338 (3%) had no test record. A total of 849,837 women were classified as attenders of whom, 95% had attended ≤ 5 years before recruitment and 89% had not had any abnormality detected at screening. **Table 5.7** shows the recruitment characteristics by screening history i.e., time since last test and previous abnormality. When compared with women with no abnormalities (regardless of time since last test), women with abnormalities were slightly more likely to be current smokers and more likely to be users of OCs and MHT. By contrast, they were less likely to be nulliparous. Women with no test record were, however, still much more likely to be nulliparous and much less likely to have used OCs or MHT compared to all groups of attenders. (see also **Table 4.2, Chapter 4**)

Broadly, the personal characteristics by abnormality were similar for analyses for risk of CIN3 where a further 31,305 women were excluded (see **Section 5.3.2.4**) and are presented in **Appendix Table C.1**

5.3.3.2 Screening history and the risk of cervical neoplasia

Results from minimally adjusted models were broadly similar to fully adjusted models for all outcomes examined i.e., CIN3, ICC and histo-types SCC and AC. Minimally adjusted RRs are presented in the figures and only fully adjusted RRs are reported in text below.

Risk of ICC

A total of 1 025 cases of ICC were diagnosed during a median follow up time of 19.6 years. **Figure 5.2** shows the association between screening history and risk of ICC, first by time since last test; then by abnormality only; and finally by previous abnormality within categories of time since last test.

When compared to good attenders, women who were poor attenders had a higher relative risk for ICC (RR: 1.89, 95% CI: 1.51-2.37). The risk of ICC was also increased with increasing severity of previous abnormality RR: 1.69, 95%

CI: 1.40-2.05 and RR: 4.21, 95% CI: 3.35-5.28 for minor and major abnormalities respectively compared to no abnormalities.

When previous abnormality was stratified by time since last test, the risk of ICC for women who had previous abnormalities was greater than that for women who had no previous abnormalities in each category of time since last test. However, the risk for ICC was highest in poor attenders with a history of abnormality (RR: 9.18, 95% CI: 5.39-15.62) (**Figure 5.2**)

Women with no test record were about 4 times more likely to develop ICC compared to either all good attenders (RR: 3.99, 95% CI: 3.18-5.01); all women with no abnormalities (RR: 4.17, 95% CI: 3.32-5.24); or good attenders with no abnormalities (RR: 4.47, 95% CI: 3.55-5.62).

Risk of CIN3

A total of 1 479 cases of CIN3 were diagnosed during a median follow-up time of 8.8 years. **Figure 5.2** shows the association between screening history and risk of CIN3.

When compared to women with no abnormalities, the risk of CIN3 increased with increasing severity of previous abnormality(RR: 2.18, 95% CI: 1.91-2.50 and RR: 4.63, 95% CI: 3.85-5.57 for minor and major abnormalities respectively). However, there was little effect of time since last test, including in joint analysis within categories of previous abnormality although this analysis had small numbers.

Histological subtypes

Of 1,025 cases of invasive cancer, 582 (57%) were SCC and 279 (28%) were AC. There was significant heterogeneity by histo-type in the association between ICC and time since last test, previous abnormality and overall screening history (heterogeneity: all $p<0.001$)

The pattern of risk for SCC associated with screening history was similar to that of overall ICC, albeit much stronger. (see **Figure 5.3**) A higher risk of SCC was found in poor attenders when compared to good attenders, (RR: 2.39, 95% CI: 1.80-3.17) and women with a history of a previous abnormality (RR: 3.01, 95% CI: 2.47-3.66 vs. no abnormalities).

When previous abnormality was stratified by time since last test previous abnormality, similar to ICC, the risk of SCC was highest in women who had previous abnormalities and were also poor attenders (RR: 10.72, 95% CI: 5.30-21.70). Finally, women with no test record were about 7-times more likely to develop SCC in all models: when compared to either all good attenders (RR: 6.48, 95% CI: 4.98-8.44); or women with no abnormalities (RR: 7.00, 95% CI: 5.36-9.14); or good attenders with no abnormalities (RR: 7.84, 95% CI: 5.98-10.27).

By contrast, associations between screening history and risk of AC were broadly null (see **Figure 5.3**). There was some evidence of an increased risk of AC associated with previous abnormality and poor attendance (RR: 6.15, 95% CI: 1.96-19.30), although based on very small numbers, with a correspondingly wide CI.

5.3.3.3 Sensitivity analyses

A similar pattern of results was seen when time since last test was altered to $\leq 3/>3$ years, albeit weaker. As in **Chapter 4**, a weakened effect suggests the selection of a 5-year window was appropriate for these analyses. (see **Appendix C, Figure C.1**)

5.3.4 Discussion

These analyses have shown a significant association between screening history, both a history of attendance and previous abnormalities, and the risk of all ICC, consistent with results from previous studies.[183–188] However, while there was an increased risk of CIN3 in women with previous abnormalities in line with previous evidence,[183] there was little evidence of an association with time since last test although numbers in these analyses were too small to answer this question definitively.

There was significant heterogeneity in cervical cancer risk associated with screening history for the two major histotypes: SCC and AC. Substantially increased risks were seen for SCC with poor attendance and a history of previous abnormality both individually and jointly (overall screening history), but there was little to no association with AC. This result is in keeping with previous reports on attendance for screening, [8] though previous studies have not reported testing for heterogeneity by previous abnormality.[185, 189]

5.3.4.1 Possible Mechanisms

Attendance for screening deliberately interrupts the natural history of cervical cancer by the detection and treatment of precursor lesions.[115] Therefore, women who do not attend for screening, do not have the opportunity for the detection of lesions and are thus more likely to develop ICC. It therefore also follows that a higher risk of precursor lesions like CIN3, would be expected in women who attend for screening although this was not seen in this study possibly due to the small number of cases. It is not unexpected, that there was little evidence of an association between screening history and invasive AC of the cervix. These cancers and their precursor lesions occur in the endocervical canal,[229] which can be difficult to sample making detection by conventional cytology methods challenging.[98, 189]

Having an abnormality detected at screening signifies an increased risk of developing cervical cancer, but this risk should be reduced with appropriate follow-up and treatment and is the key to the successful reduction in the incidence of

cervical cancer associated with screening.[16] The persistently increased risk in this study for women within an organised programme may, therefore, be due to sub-optimal clinical management (follow-up or treatment), underlying high risk or both. This investigation does not provide an analysis of clinical management of women with previous abnormality therefore cannot definitively differentiate between these possibilities. With respect to clinical management, over the screening history period the recommended follow-up in England for inadequate/borderline or mild dyskaryosis was a repeat smear at a shorter interval and women with moderate or worse dyskaryosis or a second occurrence of mild dyskaryosis were referred to colposcopy, where excisional treatment may have been performed.[162] (see **Figure 2.6, Chapter 2**) Previous evidence shows that compliance for colposcopy in the U.K is generally very high (around 93%),[230] and it is therefore likely that women who would have been referred for colposcopy would have attended for scheduled appointments. Previous evidence has also shown that previous attendance is a key factor in predicting future attendance i.e. women who attend for screening are likely to continue attending.[140] It is therefore likely that women in this cohort, who were 97% attenders at recruitment and recruited from the NHS Breast Screening Programme,[129] would also continue to attend for follow-up appointments.

Nonetheless, in this investigation, even after long-follow up and presumably treatment, women who had previous abnormalities, and particularly high-grade abnormalities, were to found to have persistently elevated risks of cervical neoplasia. This finding suggests that these women may form a subgroup with higher underlying risk. As discussed in **Chapter 2** of this thesis, given the role of HPV in aetiology, and that viral type and load correlate directly with the development and severity of abnormality,[231] these findings are likely indicative of persistent oncogenic HPV infection. This conclusion is further supported by the age of the women in this study during the screening history period (mean age 45 years at the start of the screening history period) where any HPV infections are likely to be persistent.[232] A history of screen-detected abnormalities is therefore likely to be a good proxy for persistent HPV infection. This relationship was less clear for AC in this investigation. However,

previous evidence has shown strong and significant associations between precursor abnormalities in glandular cells (atypical glandular cells) and the risk of AC.[189] Assessment stratified by type of abnormality was not possible in this investigation, and further work is therefore warranted comparing associations between the range of previous abnormalities and risk of cervical neoplasia across histo-types.

5.3.4.2 Strengths and weaknesses

This analysis has several strengths. This study lends prospective evidence in support of the recent IARC evaluation of a strong preventive association between a history of attendance for screening and invasive cervical cancer.[16] Due to the relatively large number of cases in this study, I have also been able to prospectively compare the associations with screening attendance by histological type, building on the findings of the Collaboration's 2007 meta-analysis which was largely driven by case-control studies.[8] Although the evaluation of screening using observational evidence may potentially be affected by some bias, evidence from cohort studies is generally more reliable i.e., not subject to limitations associated with case-control studies as described in **Section 5.2.4.1**

The aim of screening is to detect and subsequently effectively treat abnormalities including CIN3 thereby protecting a woman who has undergone screening from developing ICC, compared to if they had not been identified or treated, or compared to a similar group that had not undergone screening. This study contributes evidence to the limited previous literature showing a persistently elevated risk of cervical neoplasia for women with previous abnormalities within organised programmes which provide follow-up.[184, 185] This suggests a need for further evidence on the efficacy of post-screening components of care after the detection of abnormalities via screening, in this case Pap-smear based screening. Pap-smear screening has been the cornerstone of cervical cancer prevention for decades and remained the primary screening test used in most countries worldwide in 2021 even with the rapid expansion of HPV screening.[233] More in-depth studies are also necessary on whether current HPV testing on the NHSCSP[101] confers a lower long-term risk.

However, this study is observational and is therefore subject to some limitations with respect to the evaluation of screening. The major potential bias in the evaluation of screening using a cohort study is selection bias, and women in the MWS originally recruited through the NHS Breast Screening Programme may be more health conscious than women who decline invitations i.e., they may be more likely to self-select for screening and may also have lower underlying risks for ICC. This study also had no information on invitations to screening and thus could not determine if women who did not attend did not have the opportunity to attend or declined invitations, and the results should still be interpreted with caution. However, given strong and consistent associations with non-attendance found in previous evidence across different study-designs,[187, 188] it is likely the validity of these results is not undermined by bias. The lack of invitation information also means it was not possible to determine how many screens women should have attended and this analysis uses time since last test as a proxy for frequency of attendance. These analyses also do not consider screening history beyond recruitment and follow-up for the risk of CIN3 is censored at a woman's 65th birthday when she would be no longer eligible for screening as a proxy for approximate last test date. Finally, it is of note that these analyses are based on a study period of a historic nature and NHSCSP screening protocols have changed from Pap-based screening to HPV testing and further studies in the context of current practices are necessary.

5.4 Conclusions

This prospective analysis has shown that previous screening history, defined as previous attendance and abnormality, is strongly associated with risk of cervical neoplasia and the association with screening history appears to be strongest for tumours with squamous cell morphology. These results, in combination with those of **Chapter 4**, show that screening history is indeed potentially important confounding, justifying use of the current definition of screening history for adjustment in the analyses on the risk of pre-invasive and invasive cervical cancer associated with reproductive and hormonal risk factors considered in the following chapters.

5.5 Tables

Search strategy	
(#1)	(((cervical neoplasm, uterine[MeSH Terms]) OR (cervical intraepithelial neoplasia[MeSH Terms])) OR (adenocarcinoma[MeSH Terms])) OR (carcinoma, squamous cell[MeSH Terms] AND (incidence)) AND (risk of)))
(#2)	((conventional cytology) OR (Pap smear)) NOT (liquid based cytology)) NOT (HPV)) NOT (human papilloma virus)
(#3)	((cancer screening[MeSH Terms]) OR (cancer screening test[MeSH Terms])) OR (cervical screening)
	((#1) AND (#2)) AND (#3)

Table 5.1: Search strategy for literature review

Study design	Publication	Country; Organised screening	Total cases observed (expected*)/ Population	Results (95% CI)	Comment
Systematic Review	**IARC Handbook on Cancer Prevention (2005)[187]**				
Cohort	Fidler *et al.,* 1968[191]	Canada; Yes	13 (81.2)/310 000	SIR 0.16 (0.09-0.29) for observed vs. expected among women screened at least once in the programme	Expected was drawn from time before screening
	Hakama *et al.,* 1976[90]	Finland; Yes	109 (545) /406 358	SIR 0.22 (0.18-0.27) for observed vs. expected among women screened at least once in the programme	Expected was drawn from time before screening
	Magnus *et al.,* 1987[192]	Norway; Yes	178 (286.1)/45 960	SIR 0.62 (0.52-0.75) for observed vs. expected among screened women	Expected was drawn from neighbouring 5 counties before introduction of screening
	Sparen *et al.,* 1996[193]	Sweden; Yes	438/386 990	RR 0.55 (0.51-0.61) for ever vs. never screened	
	Vikki *et al.,* 1999[194]	Finland; Yes	48(94)/45 572	SIR 0.50 (0.40-0.70) for ever vs. screened	Expected from population rates during the screening period (including the screened population
	Lynge *et al.,* 2000[195]	Denmark; Yes	115/16 187	SIR 0.53 (0.42-0.67) for ever vs. screened	
Case-control	Various[196–212]	8/17 studies	NR	Pooled OR 0.34 (0.31-0.38) for ever vs. never screened	
Systematic Review	**Peirson *et al.,* 2013**[188]				
RCT	Sankaranarayanan *et al.,* 2009 [213]	India; No	152 (118)[a]/32 058	RR for overall ICC 1.34 (0.99-1.82) for single round Pap-smear vs. no test	Cluster-randomised trial in largely unscreened women with single lifetime Pap test
			58(82)[a]/32 058	RR for advanced ICC (FIGO II+) 0.75 (0.51-1.10) for single round Pap-smear vs. no test	
Cohort	Herbert *et al.,* 1996 [214]	United Kingdom; Yes	83/116 022	RR 0.38(0.23-0.63) for test in last <5.5 years vs. no tests	
Case-control	Various[185, 203, 207–209, 212, 215–220]	4/12 Yes	4781/22 697	Pooled OR 0.35 (0.30-0.41) for ever vs. never exposure to screening	Attendance for screening ranged from within the previous 3 years to a single lifetime screen

Table 5.2: Characteristics and results of studies of review studies by IARC[187] and Peirson *et al.,* [188] on risk of invasive cervical cancer in relation to attendance for screening

Abbreviations: RR, relative risk; CI, confidence interval; OR, odds ratio; SIR, standardised incidence ratio; NR, not reported; IARC, International Agency for Research on Cancer

[*] unless otherwise indicated

[a] Total cases observed in test arm (total cases observed in control arm)

Study design	Publication	Country	Total cases/ Population	Results (95% CI)
Cohort				
	Wang *et al.*, 2017[221]	Sweden	868/569 132	HR 0.42 (0.24-0.72) for screened vs. unscreened at age 61-65 in women unscreened at age 51-60
Case-control				
	Wang *et al.*, 2020[184]	Sweden	4041/115 616	OR 0.24 (0.22-0.26) for 2 rounds (3-5 years) screened vs not screened
	Castañon *et al.*, 2014[186]	United Kingdom	1341/3987	OR 0.25 (0.21-0.30) for screening interval $\leq$ 5.5y vs. not screened

Table 5.3: Characteristics and results of studies on the risk of invasive cervical cancer in relation to attendance for screening within organised screening programmes, published after May 2012

Abbreviations: HR, hazard ratio; CI, confidence interval; OR, odds ratio

Study design	Publication	Country	Total Cases/ Population	Results (95% CI)
Invasive cervical cancer				
Cohort	Nygard *et al.,* 2003[183]	Norway	231/536 698	RR 3.9 (2.1-7.2) for index ASCUS+ subsequent normal test vs. only normal tests
Case-control	Wang *et al.,* 2020[184]	Sweden	4254/120 006	OR 17.4 (13.3-22.1) for 2 abnormal vs. only normal tests
	Castañon *et al.,* 2014[186]	United Kingdom	341/3987	OR 11.52 (8.57-15.47) for abnormal vs. adequate negative tests
	Andrae *et al.,* 2008[185]	Sweden	1230/7354	OR 7.55 (5.88-9.69) for abnormal vs. normal tests
Cervical intraepithelial neoplasia grade 3 (CIN3)				
Cohort	Nygard *et al.,* 2003[183] **Outcome**: CIN2/3	Norway	3742/536 698	RR 3.6 (3.1-4.3) index ASCUS+ subsequent normal test vs. only normal tests

Table 5.4: Characteristics and results of studies included on risk of invasive cervical cancer and cervical intraepithelial neoplasia grade 3 (CIN3) in relation to previous abnormalities at screening within organised screening programmes

Abbreviations: RR, relative risk; CI, confidence interval; RR, relative risk; OR, odds ratio

Study design	Publication	Country; Organised Screening	Total Cases/Population		Results (95% CI)	
			SCC	AC	SCC	AC
Meta-analysis	The Collaboration 2007[8]	Various; 3/12 studies Yes	8097/34 542	1374/27,819	RR 0.46 (0.42-0.50) for previous Pap test vs. none	RR 0.65 (0..56-0.52) for previous Pap test vs. none
Case-control	Castañon *et al.,* 2016[190]	United Kingdom; Yes	9724/34 177	2717/27 170	OR 0.14 (0.12-0.15) for attenders <3.5 or 5.5 vs. non-attenders within <3.5 for regular attenders vs. non-attenders[a]	OR 0.46 (0.39-0.55) for regular attenders vs. non-attenders[a]
	Andrae *et al.,* 2008[185]	Sweden; Yes	921/7045	309/6493	OR 0.33 (0.29-0.40) for regular attenders vs non-attenders[b]	OR 0.63(0.47-0.83) for regular attenders vs non-attenders[b]

Table 5.5: Characteristics and results of studies included on risk of squamous cell and adenocarcinoma in relation to attendance for screening

Abbreviations: SCC, squamous cell carcinoma; AC, adenocarcinoma; RR; relative risk; OR, odds ratio; CI, confidence interval
[a] Regular attenders defined as women who had a record of screening attendance in the 3.5 (age <50) or 5.5(age 50+)years before diagnosis
[b] Regular attenders defined as women who had a record of screening attendance in the 3.5 (age <53) or 5.5(age 53+)years before diagnosis

Study design	Publication	Country	Total Cases/Population		Results (95% CI)	
			SCC	AC	SCC	AC
Cohort	Wang *et al.,* 2016[189]	Sweden	187/3 024 340	48/3 024 340	IRR 6.7 (5.1-8.9) for HSIL vs. normal tests after 10.5-15.5 years of follow-up	IRR 3.3 (1.8-6.1) for HSIL vs. normal tests after 10.5-15.5 years of follow-up
					IRR 5.1 (4.3-6.1) for LSIL vs. normal tests after 10.5-15.5 years of follow-up	IRR 2.6 (1.8-3.8) for LSIL vs. normal tests after 10.5-15.5 years of follow-up
					IRR 2.5 (0.9-6.7) for AGC vs. normal tests after 10.5-15.5 years of follow-up	IRR 9.4 (4.5-19.9) for AGC vs. normal tests after 10.5-15.5 years of follow-up
Case-control	Andrae *et al.,* 2008[185]	Sweden	921/7045	309/6433[a]	OR 8.34 (6.14-11.32) for abnormal vs. normal tests[b]	OR 6.07(3.88-9.49) for abnormal vs. normal tests[b]

Table 5.6: Characteristics and results of studies included on risk of squamous cell and adenocarcinoma in relation to previous abnormalities at screening

Abbreviations: OR, odds ratio; CI, confidence interval; IRR, incidence rate ratio; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; AGC, atypical glandular cells

[a] Non-squamous cell carcinoma used as an outcome (79% adenocarcinoma)

[b] Abnormal tests defined as atypical squamous cells of uncertain significance (ASCUS), LSIL, or HSIL in the period 0.5 – 6.5 years before diagnosis.

	% (n) of women*				
	≤ 5 years before recruitment		**> 5 years before recruitment**		
	No abnormalities (n=712 785)	**Any abnormality (n=96 207)**	**No abnormalities (n=39 222)**	**Any abnormality (n=1623)**	**No test record (n=24 338)**
Mean age at baseline (SD)	56.2 (4.4)	55.1 (4.1)	56.8 (4.6)	56.8 (4.6)	56.8 (4.6)
Most deprived tertile	32 (228 725)	34 (32 781)	38 (14 875)	40 643	40 (9812)
No educational qualifications	2 (16 553)	2 (2062)	3 (1083)	2 (39)	4 (883)
Body mass index 30+kg/m^2	17 (112 403)	16 (14 232)	23 (8458)	23 (344)	23 (5159)
Current smokers	19 (132 097)	21 (20 305)	25 (9693)	30 (481)	20 (4826)
Ever oral contraceptive use	61 (431 196)	67 (63 868)	52 (20 040)	57 (920)	31 (7480)
Ever menopausal hormone therapy use	45 (315 079)	51 (48 257)	28 (10 932)	32 (508)	18 (4194)
Nulliparous	10 (73 192)	7 (6774)	19 (7601)	13 (203)	48 (11 488)
Among parous women:					
Mean number of FTPs (SD)	2.1 (1.2)	2.3 (1.2)	2.0 (1.5)	2.0 (1.5)	2.0 (1.5)
Age at first birth <18 years	3 (16 373)	3 (2984)	3 (933)	4 (59)	3 (396)

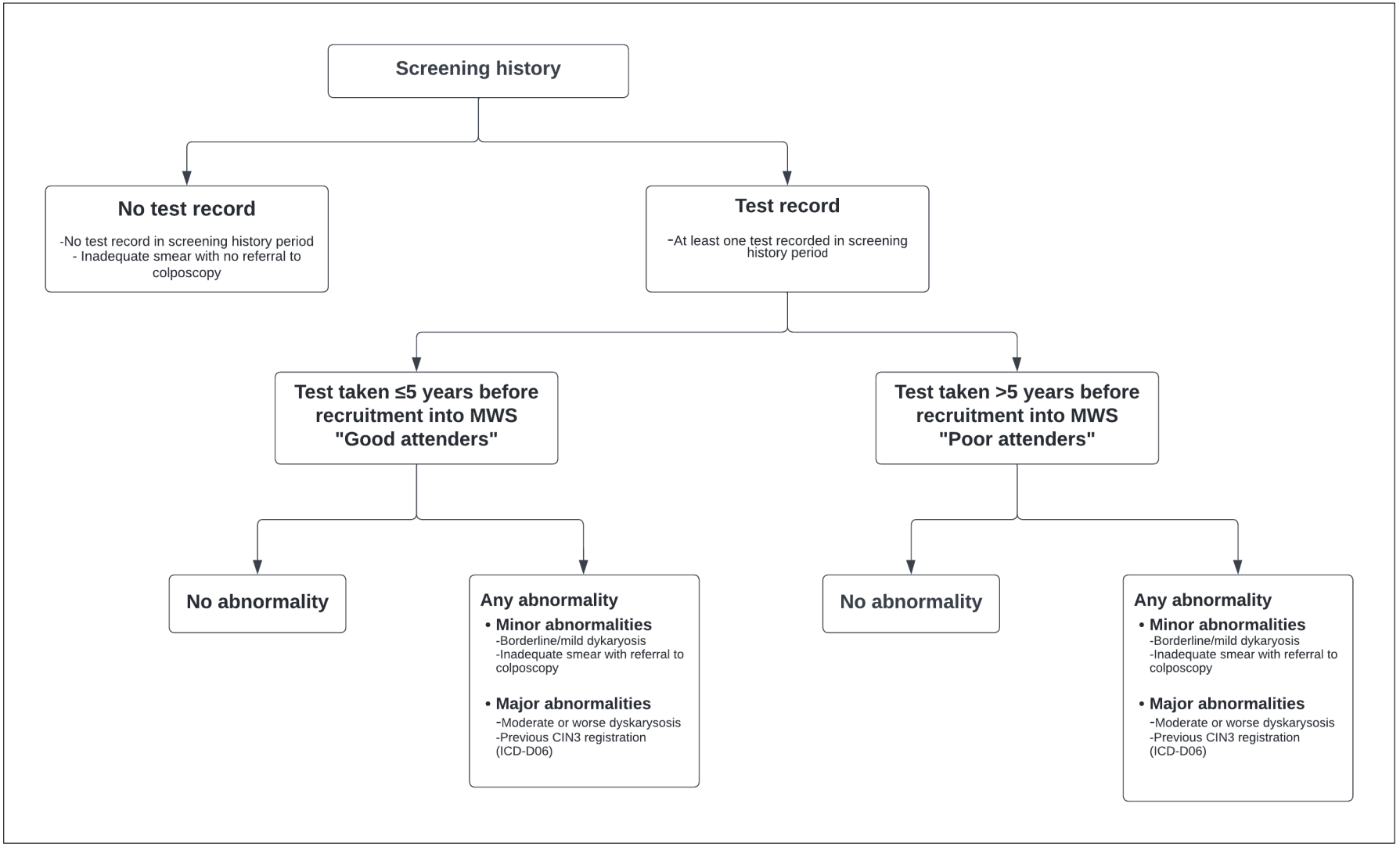
Table 5.7: Recruitment characteristics of women included in analyses of risk of invasive cervical cancer (ICC) analyses in relation to screening history defined as time since last test and previous abnormality

* unless otherwise indicated

Estimates calculated in women with no missing values

5.6 Figures

Figure 5.1: Definition of screening history based on worst cervical cytologic abnormality and attendance (time since last test) during the screening history period.



Screening history period: Period between the start of the NHSCSP (1st April 1988) and recruitment into the MWS (1996-2001
Abnormalities were determined over the entire screening history period

Figure 5.2: Minimally and fully adjusted relative risks (RR) and 95% confidence intervals (CI) of A: Invasive cervical cancer and B: Cervical intraepithelial neoplasia grade 3 (CIN3) in relation to past screening history

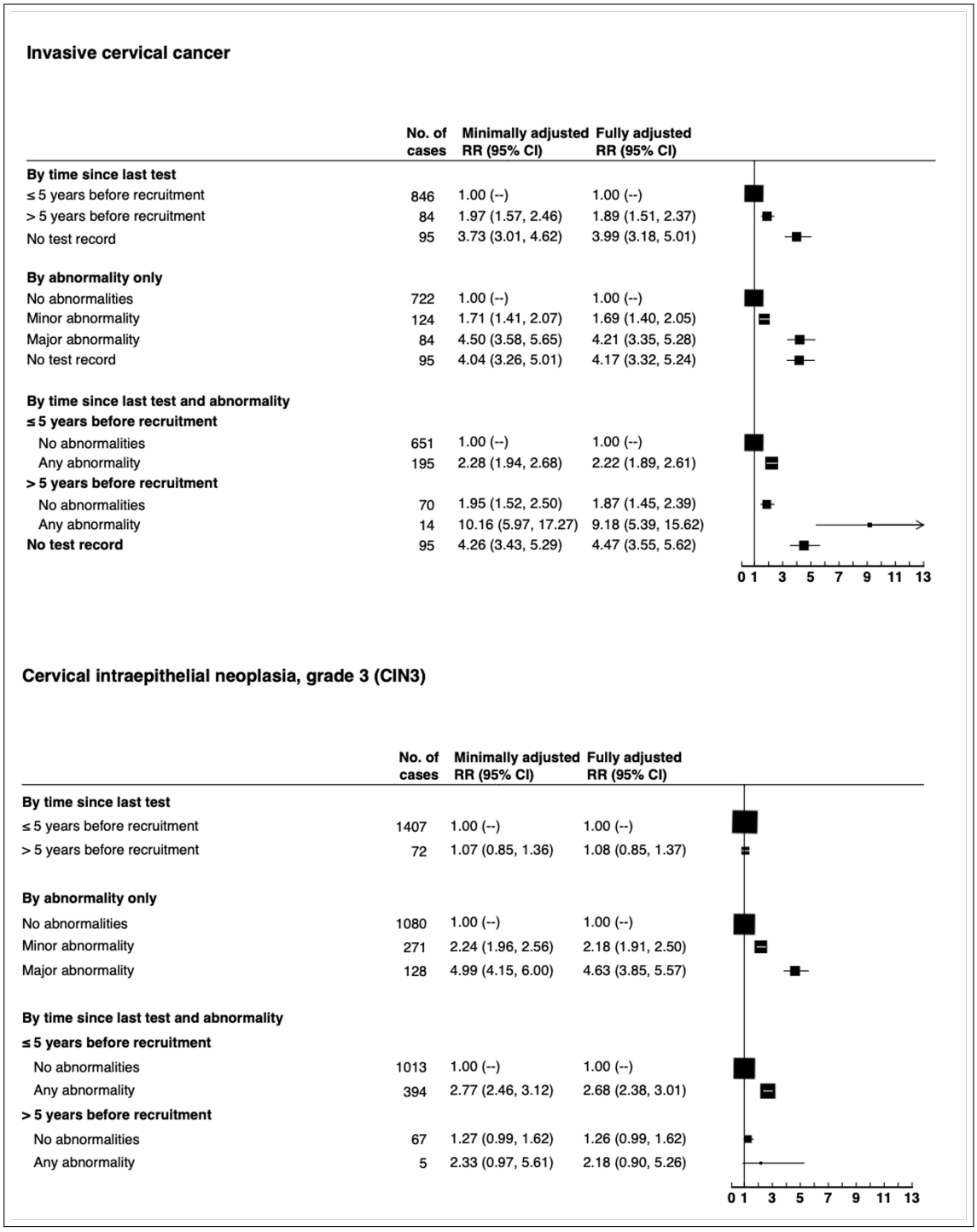
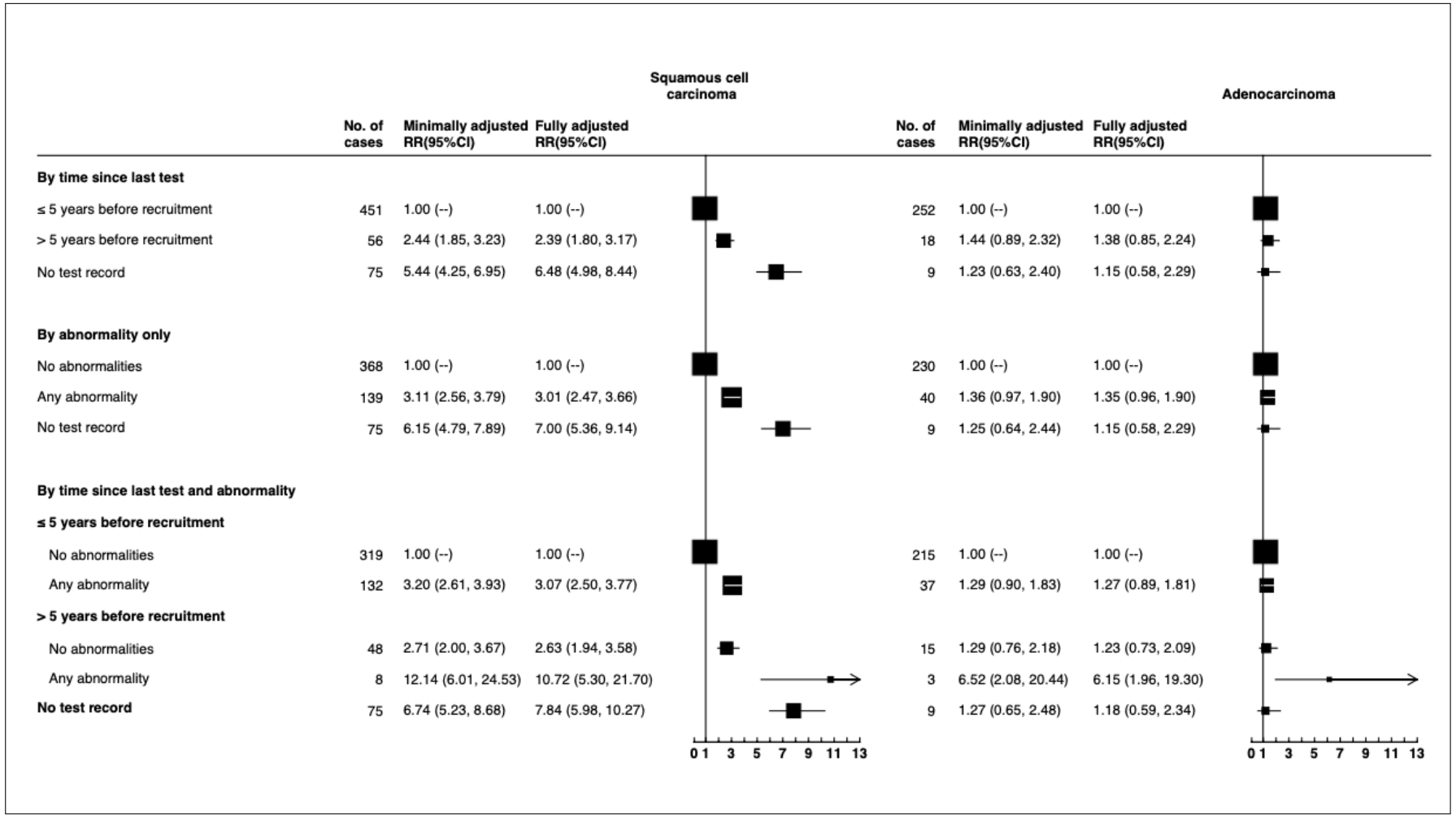


Figure 5.3: Minimally and fully adjusted relative risks (RR) and 95% confidence intervals (CI) of A: Invasive cervical cancer, squamous cell carcinoma and B: Invasive cervical cancer, adenocarcinoma in relation to past screening history



	Squamous cell carcinoma			Adenocarcinoma		
	No. of cases	Minimally adjusted RR(95%CI)	Fully adjusted RR(95%CI)	No. of cases	Minimally adjusted RR(95%CI)	Fully adjusted RR(95%CI)
By time since last test						
≤ 5 years before recruitment	451	1.00 (--)	1.00 (--)	252	1.00 (--)	1.00 (--)
> 5 years before recruitment	56	2.44 (1.85, 3.23)	2.39 (1.80, 3.17)	18	1.44 (0.89, 2.32)	1.38 (0.85, 2.24)
No test record	75	5.44 (4.25, 6.95)	6.48 (4.98, 8.44)	9	1.23 (0.63, 2.40)	1.15 (0.58, 2.29)
By abnormality only						
No abnormalities	368	1.00 (--)	1.00 (--)	230	1.00 (--)	1.00 (--)
Any abnormality	139	3.11 (2.56, 3.79)	3.01 (2.47, 3.66)	40	1.36 (0.97, 1.90)	1.35 (0.96, 1.90)
No test record	75	6.15 (4.79, 7.89)	7.00 (5.36, 9.14)	9	1.25 (0.64, 2.44)	1.15 (0.58, 2.29)
By time since last test and abnormality						
≤ 5 years before recruitment						
No abnormalities	319	1.00 (--)	1.00 (--)	215	1.00 (--)	1.00 (--)
Any abnormality	132	3.20 (2.61, 3.93)	3.07 (2.50, 3.77)	37	1.29 (0.90, 1.83)	1.27 (0.89, 1.81)
> 5 years before recruitment						
No abnormalities	48	2.71 (2.00, 3.67)	2.63 (1.94, 3.58)	15	1.29 (0.76, 2.18)	1.23 (0.73, 2.09)
Any abnormality	8	12.14 (6.01, 24.53)	10.72 (5.30, 21.70)	3	6.52 (2.08, 20.44)	6.15 (1.96, 19.30)
No test record	75	6.74 (5.23, 8.68)	7.84 (5.98, 10.27)	9	1.27 (0.65, 2.48)	1.18 (0.59, 2.34)

Women have been there, we are here now.

—Maaza Mengiste

6

Reproductive factors and the risk of cervical neoplasia

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6.1 Introduction

An association between parity and invasive cervical cancer (ICC) has long been suspected [234]. Currently, it is widely accepted based on previous observational evidence that multiparity and early age at first full-term pregnancy (FTP) are independently associated with an increased risk of ICC, despite their strong inter-relationship.[7] Risks of carcinoma *in situ* (CIS) including cervical intraepithelial neoplasia grade 3 (CIN3) associated with age at first FTP have been found to be similar, but there is no clear evidence that the risk of CIN3 is associated with multiparity, after allowing for age at first FTP. Significant risk trends have also been reported in both major histological sub-types of ICC: squamous cell carcinoma (SCC) and adenocarcinoma (AC) for increasing multiparity and decreasing age at first FTP, with a significantly greater trend for SCC versus AC for multiparity but not age at first FTP.[8] However, previous evidence has been largely retrospective and not able to adequately account for a woman's cervical screening history beyond her likelihood of having ever been screened or not.[7, 8] Previous chapters of this thesis have shown evidence of large differences in attendance for cervical screening according to reproductive factors (see **Chapter 4, Section 4.3.3.2**) and, strong associations between screening history and incident cervical neoplasia (see **Chapter 5**). Screening history is therefore likely to be substantial confounding in the associations between reproductive factors and cervical neoplasia.

In this chapter, I present the findings of a narrative review of previous evidence on reproductive factors i.e., age at first FTP and parity including number of FTPs, and the incidence of cervical neoplasia i.e., CIN3 and overall ICC, including separately by major histo-type, SCC and AC. I then report on a detailed prospective investigation of these relationships in the Million Women Study (MWS) with linked NHS Cervical Screening Programme (NHSCSP) records and almost two decades of follow-up. Specifically, this study 1) evaluates the association between reproductive factors and the risk of CIN3 and ICC overall; 2) examines the relationship between reproductive factors and invasive cervical cancer risk by tumour subtypes, SCC and

AC ; and 3) investigates the effect of adjustment for screening history, as defined in Chapter 5, on risk estimates of cervical neoplasia in relation to reproductive factors.

6.2 Literature Review

6.2.1 Objectives

This review aims to summarise previous evidence on the risk of CIN3 and ICC,including separately by major histo-type (SCC and AC), associated with reproductive factors i.e., age at first FTP and parity including number of FTPs.

6.2.2 Methods

To summarise what is known the risk of cervical neoplasia associated with reproductive factors, I first summarise the findings of two individual participant data meta-analyses underlying current perspectives on this relationship published by the International Collaboration of Epidemiological Studies of Cervical Cancers ("the Collaboration"). The first reports on an investigation of the risk of CIN3 and overall ICC associated with reproductive factors,[6] and the second explored potential variation in associations by invasive cancer histo-type.[8] I then present the findings of a literature search of online database PubMed for subsequently published evidence on reproductive factors in relation to CIN3 and ICC [September 2006-1 Aug 2022] and separately by histo-type [March 2007-1 Aug 2022]. Search strategy is detailed in **Table 6.1**.

All articles reporting relative risks (RR) and confidence intervals (CI), with adjustment at least for age, for the incidence of overall ICC, CIN3 and/or histo-types of ICC in relation to parity and/or number of FTPs; or age at first FTP were included. Results for which 95% CIs were calculated using floating absolute risks are presented as floating CIs (FCI) if conventional CI were not reported in the text. Only studies that were based on cohort or case-control studies with comparison groups and which were published as full papers in peer-reviewed journals were included. Only studies with an outcome of ICC (or histo-types SCC or AC) and CIN3 or CIN3/CIS were included with the exception of Jensen *et al.,*[235] who included CIN3+, a composite outcome including severe dysplasia, CIN3 and CIS. Studies on recurrence and/or progression of disease were not included in this review. The

minimum study size for case-control studies was at least 100 cases of ICC or at least 200 cases of CIN3/CIS and at least 30 cases for cohort studies. These criteria were defined to be similar to those used to select studies for both meta-analyses. [6, 8]

6.2.3 Results

Subsequent to the Collaboration meta-analysis,[7] a total of seven studies have been published on the risk of ICC and CIN3 associated with parity[11, 235–240] and/or age at first birth.[11, 239, 240] To my knowledge, no studies have published results on the relationship between ICC and reproductive factors separately by histo-type since the Collaboration's meta-analysis[8] which is presented in **Section 6.2.3.3**. Study characteristics and results are presented in text and in **Tables 6.2 and 6.3**.

6.2.3.1 Risk of ICC

Parity

The Collaboration included a total of 9,812 cases (<1% prospective) of ICC and 24,716 controls, after exclusion of studies with no information on sexual history. Adjusting for sexual behaviour, they reported that the risk of ICC was significantly increased with increasing number of FTPs (trend: $p<0.001$). Among parous women, additional adjustment for age at first FTP attenuated the magnitude of risks, but the risk trend remained significant with increasing number of FTPs (RR for 7+ vs. 1-2 FTPs 1.76, 95% CI: 1.53-2.02, trend: $p<0.001$). These results were not adjusted for past cervical screening history or other confounding factors including smoking status and oral contraceptive (OC) use which were reported to have made no material difference on estimates in preliminary analyses. Results were similar when analyses for the risk of ICC were restricted to high-risk HPV (HrHPV) positive cases and controls.

Six studies have subsequently reported on the risk of ICC in relation to parity.[11, 236–240] (see **Table 6.2**). Two studies[11, 237] reported on the risks in all women i.e., parous vs. nulliparous, while the remaining four studies[236, 238–240] reported on analyses restricted to parous women only. In the first study based on an analysis

of the European Prospective Investigation Cancer and Nutrition (EPIC) cohort, Roura *et al.,* aimed to prospectively examine reproductive risk factors for ICC.[11] After a median of 9 years of follow-up, 261 cases of ICC were diagnosed in the cohort of 308,036 women of whom, almost half had had 2 FTPs. They found a non-significant reduction in risk of ICC in women who had ever had a FTP compared to those who had not (RR 0.7, 95% CI: 0.5-1.0), with no significant risk trend for ICC with increasing parity in contrast to the Collaboration (trend: p=0.4). There were also no associations found for the risk of ICC when analyses were restricted to parous women only, although data were not given. No adjustment for screening or sexual history was reported in this study but models were adjusted for a number of personal factors as in **Table 6.2**. Findings on parous vs. nulliparous women were broadly similar in a nested case-control study adjusted for HPV serological markers, but the risk of ICC was found to significantly increase with increasing parity (trend: p=0.02). However, this analysis included small numbers (n=123, with 16 in highest category 4+ FTP) with correspondingly wide CIs and individual estimates did not reach statistical significance. When this analyses was further restricted to only HPV-positive controls, there was no significant risk trend for ICC with increasing number of FTPs (trend: p=0.3). (Data not shown in **Table 6.2**)

Thulaseedharan *et al.,* reported on a cohort of 30,958 women aged 30-59 years based within the control arm of a screening trial in India in which women had a mean parity of 4 (SD 0.2), defined as number of pregnancies. After an average of 6 years of follow-up a total of 158 cases of ICC were diagnosed and they found a significantly increased risk of ICC with increasing parity, but only 3 women were in the referent nulliparous category in this cohort with resultant wide CIs. It is also unclear whether the trend estimate included nulliparous women. (RR vs. nulliparous 95% CI: 4.6, 95% CI: 0.64-33.4 for 1-3 pregnancies [87 cases] and 7.1, 95% CI: 1.0-51.8 for 4+ pregnancies [68 cases], trend: p=0.002).[237] Analyses were adjusted for age at marriage as a proxy for age at first sexual intercourse. Adjustment for screening was not possible as these control women only received health education

on symptoms of cervical cancer and as there is little cervical screening in India women they were also unlikely to have ever had any screening.[213]

Four studies examined the risk of ICC associated with higher parity among parous women only. Paltiel *et al.,* compared the risk of reproductive cancers between women with parity of 1-4 i.e., 1-4 live-born children, and grand-multiparae i.e., women with parity of 5+, in 27,949 women aged 13-55 recruited as part of the Jerusalem Perinatal Study Cohort.[236] From a total of 74 cases of ICC, and adjusting for age at first birth, ethnic origin and education, they found no significant differences in the risk of ICC between parity groups (RR 0.77, 95% CI: 0.45-1.34 for parity 5+ vs. 1-4).

Based on 3,450 cases and 5,709 controls from the Johannesburg Cancer Study (JCS), Singini *et al.,* examined the risk of ICC associated with reproductive factors among other risk factors towards ranking established risk factors in order of priority.[238] Data from the JCS was also included in the Collaboration meta-analysis,[7] however, the study had accrued over 2500 additional cases in the more recent publication. Adjusting for only socio-demographic factors as listed in **Table 6.2**, they found an increased risk of ICC in women with higher vs. lower parity i.e., number of children (OR 1.25, 95% CI:1.07-1.46 for parity 3+ vs. 1-2). Although, they reported a significant trend in this association (trend: p=0.002), it is unclear if missing data were included in this calculation. Similar to the meta-analysis, more women in this study had higher vs. lower parity, in this case parity 3+ vs. 1-2 (65% vs. 32% for cases and 57% vs. 35% for controls).

Multiparity was also common in the study by Thakur *et al.,* based in rural India where 77.8% of women had parity of 3+, defined as number of children, and a significant risk of ICC was reported for women with higher vs. lower parity when comparing 226 cases and an equal number of controls (OR 1.70, 95% CI:1.26-2.65 for parity 3+ vs. <3).[240] This study had no information on screening history, but analyses were adjusted for age at first marriage as a proxy for sexual history.

Fewer women had high parity in the Scottish study by Pasdar *et al.,* where majority of women (60%) had parity under 3 i.e. less than 3 pregnancies of

normal duration. Based on 152 cases and 152 controls, they found a non-significant increase in risk of ICC for women with parity 3+ versus 1, but no risk trend was reported (OR, 1.37, 95%CI: 0.73-2.56 for parity 3+ vs. 1 pregnancies). This study also had no information on women's past screening history, but analyses were adjusted for age at first delivery.

Age at first FTP

The Collaboration found that compared to nulliparous women the risk of ICC was increased with decreasing age at first FTP in models adjusted for sexual behaviour (RR 2.62, 95% FCI: 2.16-3.17 for <16 vs. nulliparous women, trend:p<0.001). The trend remained significant, after additionally controlling for number of FTPs among parous women, and compared to women with age at first FTP at 25+ years the relative risk for age at first FTP in the lowest category (age <17 years) was 1.77, 95% CI: 1.42–2.23, trend: p<0.001. Results were also broadly similar in analyses restricted to HrHPV positive cases and controls.[7]

Subsequent to the meta-analysis, only three studies have been published on age at first FTP and the risk of ICC.[11, 239, 240] In the EPIC cohort, based on a total of 189 cases with information on age at first FTP, Roura *et al.,* found no significant risk trend for ICC with decreasing age at first birth (trend: p=0.8) in contrast to the meta-analysis. There was also no significant trend in risk of ICC in the case-control analysis adjusted for HPV.[11] Pasdar *et al,* reported that compared to women in the lowest age group, the risk of ICC was lower in women who were older at first delivery, although it did not appear there was a linear decline in odds with increasing age at first delivery and no test for trend was reported. (ORs vs. ≤ 20 at first delivery: 0.23, 95%CI: 0.12-0.46 for ages 21-25 and 0.37, 95%CI: 0.16-0.86 for ages 26-30 at first delivery).[239] Thakur *et al.* also found that the odds of ICC were significantly lower in women who were older vs. younger at birth of first child in models adjusted for among other factors, parity and age at first marriage (OR for 19+ vs. <19 years at birth of first child: 0.34, 95%CI: 0.28-0.54).[240]

6.2.3.2 Risk of CIN3

Parity

In the Collaboration, based on a total of 4,623 cases and 21,361 controls included in analyses (23% prospective), the risk of CIN3/CIS was significantly increased with increasing number of FTPs in analyses adjusted for sexual behaviour as shown in **Table 6.3** (RR 1.60, 95%CI 1.24-2.08 for 7+ FTPs vs. nulliparous; trend: p<0.001). However, no significant trend was found after additionally controlling for age at first FTP among parous women (trend: p=0.27). Results were similar when analyses for risk of CIN3 were restricted to HrHPV positive cases and controls.

Two studies have since published findings on the risk of high-grade precursor lesions. Roura *et al.,* reported that the risk of CIN3/CIS was significantly increased with increasing number of FTPs in the main EPIC analysis based on 804 cases (trend: p=0.03), and the RR for 4+ FTPs compared to nulliparous women was 2.3, 95% CI: 1.6-3.3. This association was also reported to remain significant when analyses were restricted to parous women only, and adjusted for age at first birth, although data were not given. There was no significant risk trend for CIN3/CIS in the nested case-control analysis adjusting for HPV (trend: p=0.2) or in analyses restricted to HPV positive controls (trend: p=0.2), although there was still evidence of an association for women who had ever had an FTP compared to those who had not in these analyses.[11]

Jensen *et al.,* used a composite outcome measure of CIN3, CIN3+, which was defined as histologically diagnosed severe dysplasia and carcinoma *in situ* or similar cytological diagnoses without histological confirmation.[235] After approximately 13 years of follow-up of 1,353 women with HrHPV at baseline, 17.8% of women developed CIN3+ and a borderline significant association between ever giving birth and the risk of CIN3+ was reported (RR:1.39, 95% CI: 1.02-1.91) compared to nulliparous women in models adjusting for smoking status, length of schooling, and HPV16. However, there were no statistically significant associations for either 1 or 2+ births compared to nulliparous women and no test for trend was reported.(see **Table 6.3**)

Age at first FTP

In the Collaboration, from a total of 3,618 cases (17% prospective) and 17,488 controls with information on sexual history included in analyses, decreasing age at first FTP was significantly associated with increasing risk of CIN3/CIS when compared to nulliparous women ($p<0.001$). The risk associated with age at first FTP was unaffected by controlling for the number of FTPs among parous women and the trend remained significant with the highest relative risk seen in women <17 years compared to those 25+ years at first FTP (1.78, 95% CI: 1.26-2.51; trend: $p<0.001$).[7]

Since the Collaboration, to my knowledge, only Roura *et al.,* have published findings on age at first FTP and the risk of CIN3/CIS.[11] They found no significant trend with decreasing age at first FTP in the main cohort analysis (RRs vs 30+ years at first FTP, 1.1 95% CI: 0.8-1.4 for ages 25-29 and 1.2, 95% CI: 0.9-1.7 for age ≤20 years, trend: $p= 0.2$). A significant trend was however reported for the same comparison in the nested case-control adjusting for HPV serology ($p=0.03$), but this was based on small numbers in each category with null RR estimates with wide CIs.

6.2.3.3 Histological subtype

Parity

Based on a total of 8,097 cases of SCC, 1,374 cases of AC and 26,445 controls, the Collaboration reported that the RRs for both histological types significantly increased with increase in number of FTPs in analyses adjusted for number of sexual partners, age at first intercourse, smoking status, Pap smears and duration of OC use (RRs vs. nulliparous: 2.08, 95% FCI: 1.95-2.23 and 1.61, 95% FCI: 1.37-1.90 for 5+ FTPs for SCC and AC respectively; trend in parous women: $p<0.001$). In a case-case comparison of SCC and AC, the risk trend was also significant (trend: $p=0.01$) suggesting significant variation in the risk associated with number of FTPs by histo-type.[8]

Age at first FTP

Younger age at first FTP was also associated with both AC and SCC (RRs vs. 25+ years at first FTP: 2.72, 95%CI: 2.42-3.05 and 2.01, 95%CI: 1.53-2.65 for age <17 years at first FTP for SCC and AC respectively; trend in parous women: $p<0.001$). However, in the case-case comparison of SCC and AC, there was no significant trend in risk (trend: $p=0.1$) suggesting no heterogeneity by histo-type.[8]

As mentioned in **Section 6.2.3**, to my knowledge no studies have been published subsequently that explore possible heterogeneity in risk of ICC by histotype in relation to reproductive factors.

6.2.4 Discussion

The Collaboration's meta-analysis supports an independent association between both higher parity and early age at first FTP and an increase in the risk of ICC that remains significant among parous women after mutual adjustment.[7] They also provide evidence that whereas a significant relationship exists between the risk of CIN3/CIS and decreasing age at FTP after adjustment for sexual behaviour variables, there is no evidence that the risk of CIN3 is increased with increasing parity among parous women after additional adjustment for age at first FTP. These findings were reported to remain largely similar when analyses were restricted to HrHPV positive women. The Collaboration has also reported that the risk of ICC varies significantly between histo-types by number of FTPs; compared to women without ICC, the risk of both SCC and AC increases with increase in number of FTPs but with a significantly greater trend for SCC compared to AC. However, they found no heterogeneity by histo-type for the risk of ICC associated with age at first FTP. [8]

For the most part, the findings in the more recently published studies broadly correspond to those in the meta-analysis for the risk of ICC associated with number of FTPs[238–240] and age at first FTP[239, 240]. For the risk of CIN3, a similar pattern to the meta-analysis was reported for number of FTPs[11, 235] but not age at first FTP, where no significant associations were reported although these findings were based on much smaller numbers than the Collaboration analyses. [11] To my

knowledge, no findings on the risk of ICC histo-types associated with reproductive factors have been published since the Collaboration meta-analyses.

The findings in the meta-analysis on the risk of ICC and CIN3/CIS are, however, largely derived from retrospective studies and excluded almost all the prospective data, because only one cohort study had information on measures of sexual behaviour: number of lifetime sexual partners and age at first sexual intercourse.[241] As such, the meta-analysis only included 42 prospective cases in analysis of the risk of ICC from a total of over 10,000, and 129 of CIN3/CIS from a total of over 5000. Retrospective studies are increasingly recognised as misleading, and substantial heterogeneity between study designs has been demonstrated in their other publications on the risk of cervical cancer associated with other exposures including current smoking[73] and oral contraceptive use in non-recent users.[6]

Previous studies have also been limited in their ability to assess the effect of cervical screening history, and where available, information on screening history has been generally self-reported which is known to be imprecise.[242] For example, The Collaboration meta-analysis classified women by ever vs. never Pap smear which was largely self-reported, or where individual screening information was not available, based on knowledge of the availability of screening in the country where each study was conducted.[6] No subsequently published study reported an adjustment for screening history. Reproductive factors have been shown in previous literature,[153, 156, 158–160] as well as **Chapter 4** of this thesis, to influence screening attendance. For example, this thesis suggests that screening uptake is much greater (seven-fold) in parous than in nulliparous women. There was also evidence that women with higher versus lower parity and women who were younger versus older at first FTP were about 20% more likely to not attend. (see **Table 4.5, Chapter 4**) Therefore, previous studies may well have adjusted inadequately for this potentially major confounding factor. For example, the lack of association seen in the EPIC analyses is suggested to be as a result of negative confounding by screening.[11]

The Collaboration have reported that some associations between reproductive factors and cervical cancer varied by histotype,[8] although this conclusion is also

largely driven by retrospective evidence and with limited adjustment for cervical screening history. Previous evidence,[98, 190] as well as **Chapter 5** of this thesis, also suggests that cytology based screening is less effective in detecting early AC compared to SCC which may be due to difficulty sampling endocervical cells, where AC occurs. As such, the role of potential confounding by screening history in the analysis of risk factors for SCC vs. AC screening warrants further investigation.

There is therefore a need for new prospective large-scale evidence on the role of reproductive factors in cervical cancer and risk by cervical cancer histotype, investigating in more detail the effect of past cervical screening history on these associations.

6.3 Reproductive factors and the risk of cervical neoplasia

6.3.1 Objectives

The analysis that follows will examine the risk of ICC, CIN3, SCC and AC in relation to reproductive factors (parity and age at first FTP), taking into account past screening history as defined in previous chapters.

6.3.2 Methods

6.3.2.1 Study cohort

Data were obtained from the MWS with linked NHSCSP records. The methods of recruitment, data collection, follow-up, and ascertainment of cervical cancer for the MWS; and extraction of and linkage NHSCSP screening data have been described in detail in **Chapter 3**.

A total of 874,175 women were eligible for inclusion for the analyses of the risk of ICC and 843,389 for the risk of CIN3 (see **Chapter 3, Section 3.6.1**). For analysis of each main exposure of interest, women were excluded if they had missing data on that variable and for each adjustment variable missing values were assigned a separate category.(see **Chapter 3, Section 3.6**) For analyses on parity and number of FTPs, 3,429 women with missing information on parity were excluded in analyses for the risk of ICC and 3,711 for analyses for the risk of CIN3. For age at first FTP, 20,123 and 19,469 women with missing information were excluded for analyses of the risk of ICC and CIN3 respectively.

6.3.2.2 Exposure variables

The questions used to assess reproductive factors in this cohort have been described in **Chapter 3**. Parity was defined by the number of FTPs i.e. pregnancy that lasted $\geq$ 26 weeks.

Analyses examined the following exposures from the recruitment questionnaire: parity (parous vs. nulliparous); number of FTPs (0, 1, 2, 3, 4+) in all women and

(1,2,3,4+) among parous women; and age at first FTP (nulliparous, 25+, 21-24, $\leq$ 20 years) and among parous women (25+,21-24, $\leq$ 20 years).

6.3.2.3 Outcomes

The main outcomes of interest were cervical intraepithelial neoplasia, grade 3 [CIN3] (International Classification of Diseases 10th Edition [ICD-10] code D06) and invasive cervical cancer (ICD-10 code C53). For analyses of histotype, the outcome was split into the two most common histological groups: squamous cell carcinoma and adenocarcinoma by combining ICD-10 codes with ICD for Oncology, 3rd Edition morphology codes. For details on ascertainment of outcomes, please refer to **Chapter 3, Section 3.5**.

6.3.2.4 Statistical analysis

Women contributed person-years from the date of recruitment until the earliest of the date of invasive cancer registration, date of death or loss to follow-up, or the last date of follow-up (31 December 2018). For analysis of risk of CIN3, follow-up was additionally censored at a woman's 65th birthday as she would no longer be eligible for routine screening on the NHS Cervical Screening Programme (NHSCSP). Cox proportional hazard regression models, with time in study as the underlying time variable, were used to calculate hazard ratios (referred to as relative risks (RRs)) and corresponding 95% confidence intervals (CIs) of CIN3/ICC. Tests for trend used the categorical variable coded by the median value in each group. Tests of heterogeneity in the relationship between invasive cervical cancer and parity or age at first FTP by histo-type were performed using a competing risks approach. [19] **(see Chapter 3 Section 3.6)**

All analyses were stratified by year of birth and year of recruitment and adjusted for region of recruitment, socioeconomic status (SES), education, smoking status, body mass index (BMI), use of oral contraceptives (OC), use of menopausal hormone therapy (MHT) and for individual screening history. For details on coding of adjustment variables, please refer to **Chapter 3 Section 3.6.2**. Analyses were then restricted to parous women only and adjusted for number of FTPs (1,2,3,4+)

or age at first FTP (25+, 21-24,≤ 20), as appropriate. Relative risks adjusted for SES and region of recruitment only are referred to as RR1; those additionally adjusted for education, smoking status, BMI, OC and MHT use are referred to as RR2; and those additionally adjusted for screening history are referred to as RR3. Finally, relative risks as in RR3 and adjusted for number of FTPs or age at first FTP are referred to as RR4.

6.3.3 Results

6.3.3.1 Study participants

After exclusions, I had information on 870,746 women for analyses of the risk of ICC associated with parity, with a mean age at recruitment of 55.6 years (standard deviation [SD] 4.4). Overall, 88.6% of participants were parous i.e., reported at least one FTP. **Table 6.4** shows the characteristics of the study population, by parity. Nulliparous women were primarily more likely to have no screening record (12% vs. 2%). On the other hand, parous women were more likely to have lower educational qualifications (44% vs. 34%); to have used the oral contraceptive pill (62% vs. 47%); and slightly more likely to have used menopausal hormones (44% vs. 41%) compared to nulliparous women. Due to additional exclusions, I had information on 839,678 women for CIN3 analyses on parity, with broadly similar characteristics as presented in **Appendix D Table D.1**

Appendix Tables D.2 and D.3 show baseline characteristics in analyses for the risk of ICC by number of FTPs and age at first FTP (n= 854,052) respectively. Women with lower vs. higher parity (1 vs. 2+ FTP) were largely similar. By contrast, there were larger differences between women by age at first FTP and compared to women who were older at first FTP (25+ years) women who were of younger age (< 25 years) were from lower socioeconomic backgrounds (38% vs. 25%); less educated (54% vs. 30%); and were more likely to be obese (19% vs. 15%) and current smokers (23% vs. 14%). I had information on 823,920 women for CIN3 analyses on age at first FTP, with broadly similar characteristics.

6.3.3.2 Reproductive factors and the risk of cervical neoplasia

The effects of adjustment for screening history (RR2 to RR3) and age at first FTP or number of FTPs (RR3 to RR4) are shown in the figures and are discussed below. The following text presents maximally adjusted RRs i.e, RR3 (adjusted for screening) in all women, and RR4 (adjusted for age at first FTP or number of FTPs as appropriate) among parous women.

Risk of ICC

After a median follow-up of 19.6 years, 1,022 cases of ICC were registered. Overall, parous women had a borderline significant increase in risk of ICC compared to nulliparous women (RR:1.22, 95%CI: 1.00-1.50) as shown in **Figure 6.1**, and the risk of ICC significantly increased with increasing number of FTPs (trend: p=0.002). The risk trend remained significant in analyses restricted to parous women only after adjustment for screening history [RR3] (trend:p=0.02), but after additional adjustment for age at first FTP [RR4], there was no significant trend in risk of ICC with number of FTPs (trend: p=0.4)

The risk of ICC was significantly increased with decreasing age at first FTP (trend: p< 0.001), and the trend remained significant, among parous women (trend: p<0.001 [RR3]), and after additional adjustment for number of FTPs with RRs vs. age at first FTP 25+: 1.37, 95%CI: 1.16-1.62 for age 21-24 and 1.83, 95%CI: 1.51-2.22 for age $\leq$ 20 at first FTP; trend: p<0.001 [RR4].

Risk of CIN3

A total of 1,468 cases of CIN3 were diagnosed during a median follow up time of 8.8 years. Parous women had a 36% higher risk of CIN3 (95% CI: 1.12-1.67) compared to nulliparous women. The risk of CIN3 was significantly increased with number of FTPs compared to nulliparous women (RRs vs. nulliparous women 1.34, 95%CI: 1.05-1.70 for 1 FTP; 1.24, 95%CI: 1.01-1.53 for 2 FTPs; 1.49, 95%CI: 1.19-1.85 for 3 FTPs; and 1.70, 95%CI: 1.34-2.16 for 4+ FTPs, trend: p<0.001). The risk trend remained significant among parous women after adjustment for screening

history [RR3] (trend: p=0.01) and in models additionally adjusted for age at first FTP [RR4] (trend: p=0.01) (see **Figure 6.2**)

Similar to ICC, the risk of CIN3 was significantly increased with decreasing age at first FTP, (trend: p<0.001) and the trend remained significant among parous women (trend: p=0.001 [RR3]) and after additional adjustment for number of FTPs (trend: p=0.02 [RR4]) (see **Figure 6.2**)

Histological subtypes

Of the 1,022 cases of ICC, 57% (n=581) were squamous cell and 27% (n=278) were adenocarcinoma. There was no significant heterogeneity in the association between SCC and AC both in analyses in all women (heterogeneity: p=0.5) and among parous women only (heterogeneity: p=0.7). There was also no evidence of heterogeneity in the associations with age at first FTP between SCC and AC both in analyses in all women (heterogeneity: p=0.6) and among parous women only (heterogeneity: p=0.9). (see **Figure 6.3**)

Effect of adjustment

Screening history

Adjustment for screening history resulted in a susbtantial increase in the RRs of ICC associated with reproductive factors when parous women were compared to nulliparous women. For example, the RRs for 4+ FTPs vs. nulliparous women were 1.33, 95%CI: 1.04-1.69 and 1.62, 95%CI: 1.26-2.08; and RRs for age at first FTP $\leq$ 20 vs. nulliparous women were 1.43 95%CI: 1.14-1.79 and 1.75, 95%CI: 1.38-2.22 before and after adjustment for screening history.

A lesser effect was seen with adjustment for screening history for the risk of CIN3, with about a 10% reduction in RRs associated with both number of FTPs (RRs for 4+ FTPs vs. nulliparous women 1.82, 95%CI: 1.43-2.31 and 1.70, 95%CI: 1.34-2.16 before and after adjustment) and age at first FTP (RRs for age at first FTP $\leq$ 20 vs. nulliparous women 1.63, 95%CI: 1.30-2.03 and 1.52, 95%CI:1.22-1.90 before and after adjustment).

The largest effect of adjustment for screening history was seen when parous women were compared to nulliparous women for the risk of developing SCC in analyses stratified by histo-type, with about a 50% increase in RRs. For example, the RRs for 4+ FTPs vs. nulliparous women were 1.34, 95%CI: 0.96-1.86 and 1.81, 95%CI: 1.29-2.54; and RRs for age at first FTP ≤ 20 vs. nulliparous women were 1.52, 95%CI: 1.12-2.07 and 2.08, 95%CI: 1.51-2.86 before and after adjustment for screening history. However, adjustment for screening had little effect on risk estimates for adenocarcinoma. Adjustment for screening history also did not appreciably alter the associations for any outcome in analyses restricted to parous women only (see **Figures 6.1-6.3**), which suggests that differences in screening attendance between parous and nulliparous women seen in **Chapter 4 (see Table 4.5**) may underlie confounding effects.

Reproductive factors

Adjustment for age at first FTP resulted in a loss of significance in the association between number of FTPs and risk of ICC, after which no significant trend was found with increasing number of FTPs among parous women. On the other hand, relative risk estimates for age at first FTP were not meaningfully altered by the adjustment of number of FTPs for all outcomes but CIN3, where there was some attenuation of RRs after adjustment. As age at first FTP has been suggested to be a good proxy for sexual history (see **Section 6.3.4.3**), these findings suggest sexual history may underlie associations.

6.3.4 Discussion

6.3.4.1 Overall findings

This prospective analysis has investigated the risks of cervical neoplasia associated with parity and age at first FTP, adjusting for screening history. After almost 20 years of follow-up, the main findings in this study are as follows: 1) relative risks of ICC significantly increased with decreasing age at first FTP after adjustment for number of FTPs, but there was no clear evidence that the risk of ICC increased

with increasing number of FTPs after adjustment for age at first FTP among parous women; 2) relative risks of CIN3 significantly increased with decreasing age at FTP after adjustment for number of FTPs, and the risk trend for CIN3 associated with increasing number of FTPs remained significant after adjustment for age at first FTP among parous women; 3) neither the increase in risk of cervical cancer seen with increasing number of FTPs nor decreasing age at first FTP varied significantly between the histological types, both in all women and among parous women only; and 4) when comparing parous to nulliparous women adjustment for screening attenuated estimates for the risk of CIN3 and considerably strengthened estimates for the risk of ICC, with the strongest increase seen for tumours of squamous morphology. Adjustment for screening had no effect on estimates among parous women only.

6.3.4.2 Comparison with previous evidence

Globally, the literature supports an association between high parity and an increased risk of both ICC[7, 237, 238, 240] and high-grade precursor lesions including CIN3,[7, 11] similar to the findings of this study. Similarly, an inverse association with age at first FTP and the risk of ICC has been reported in previous literature including the Collaboration meta-analysis[7] and subsequently published studies.[239, 240]

However, in contrast to the meta-analysis, there was no clear evidence of an association between increasing number of FTPs and risk of ICC among parous women in these analyses, after adjustment for age at first FTP. These analyses based in the UK included few women with parity greater than 1 or 2 children and therefore had lower power with increasing multiparity categories which may explain the lack of association. In the Collaboration, as in subsequently published studies[238, 240], the majority of cases of ICC were women with parity over 3+ allowing more robust analyses in higher categories of parity. The same line of reasoning may apply to the lack of association seen for the risk of CIN3 among parous women in the Collaboration analyses. In this case, the Collaboration was limited in numbers of CIN3/CIS in the higher categories of parity. CIN3/CIS is detected at screening and thus majority of the cases came from developed countries

i.e., those with access to cervical screening. Analyses by the Collaboration for the risk CIN3/CIS therefore included fewer women with 3+ FTPs which may explain the lack of association with increasing parity.

The Collaboration has also previously reported a direct relationship between the risk of ICC and number of FTPs, and an inverse one with age at first FTP for both SCC and AC, with significant variation between the two for the former. This finding is in contrast with these results which showed no evidence of heterogeneity between histo-types for either relationship. The reason for the difference is not clear, although as mentioned this investigation has included fewer numbers in higher categories of parity than the Collaboration. Additionally, the Collaboration analyses on histo-type in relation to number of FTPs did not adjust for age at first FTP, with potential risk of confounding. More evidence from other studies and populations would be needed to clarify this association.

Previous studies, including the study by the Collaboration, have been limited in their ability to take account of previous screening history as discussed in **Section 6.2.4**. The findings in this investigation i.e., the considerable effect of adjustment for screening when comparing parous to nulliparous women, are therefore fairly novel. These findings are likely driven by the large differences in attendance between nulliparous and parous women in shown in **Chapter 4**. Although differences in screening attendance by parity have been demonstrated previously, the differences in this cohort were much more striking and may reflect specific (unknown) differences in this group.

6.3.4.3 Possible mechanisms

Several possible biological mechanisms explaining these potential associations have been hypothesised. First, the high concentrations of endogenous oestrogens during pregnancy, have been suggested to potentially initiate or accelerate cervical carcinogenesis in a similar manner to exogenous hormones like oral contraceptives.[243] Studies in transgenic mice have shown a synergistic interaction between oestrogen, oestrogen receptors and HPV oncoproteins causing cervical cancer.[9, 138] (see

Chapter 2, Section 2.2.1.1) A role for hormones is also supported by evidence showing an increased risk of ICC in women with previous full-term pregnancies but not in women who had earlier terminations of pregnancy, as hormonal levels increase sharply towards the end of pregnancy.[5] A second hypothesis for the association with parity is pregnancy induced immuno-suppression predisposing women to either HPV acquisition, persistence, or oncogenic progression.[137] In support of this, there is some evidence to suggest increased detection of HPVs in pregnant women[244] and research in molecular biology has also found the enhanced expression of the HPV gene during pregnancy.[245] Finally, trauma during vaginal delivery is also hypothesised to play a role.[135, 136] During pregnancy and delivery, there is outward turning of the inner "endocervix" towards the outer "ectocervix" (see **Figure 2.1, Chapter 2**), with increased exposure of the transformation zone where HPV infections tend to occur.[4, 21] This is further supported by the lack of excess risk of cervical cancer in women who delivered via caesarean section compared to those who delivered vaginally reported by the Collaboration.[7] However, as previous studies do not report increased risks in still births or termination of pregnancy some uncertainty remains about how much this process influences risk.[135]

Previous sexual history may also explain observed associations with age at first FTP. This is because in populations where the gap between AFSI and age at FTP is likely to be short, such as in older women as in the MWS, these variables have been shown to be strongly interrelated. For example, the Collaboration showed that while there was some attenuation of the association for number of FTPs after adjustment for sexual behaviour (number of sexual partners and AFSI), there appeared to be a greater attenuation after additional adjustment for age at first FTP.[7] Adjustment for age at FTP also attenuated the magnitude of estimates in my analyses and is therefore likely to be a good proxy for sexual initiation, which has been reported previously.[246]

6.3.4.4 Strengths and weaknesses

The major strength of this analysis is that this study for the first time has been able to evaluate the confounding effect of past screening history. In this study we found that, when comparing parous to nulliparous women, estimates for the risk of ICC associated with both number of FTP and age at first FTP were strengthened by the adjustment for screening history, particularly for tumours of squamous morphology. Previous studies including the meta-analyses, have generally had limited information on past cervical screening history, because information was generally from retrospective studies and self-reported. Although it is possible the large effect in my analyses may reflect some specific unknown attributes of nulliparous MWS women, further research is needed particularly in areas of the world where multiparity and early age at first birth are common as it is possible that estimates for cervical neoplasia in the Collaboration analyses are underestimated.

Another strength is the prospective design of this study minimising the potential for selection bias which is a potential weakness of particularly hospital based case-control studies (68% of cases in Collaboration). In this case, it is possible that women in control groups would have had conditions that would have changed their screening activity compared to cases. The large sample size also makes possible the first prospective analyses by cervical cancer histo-type to my knowledge. Finally, the MWS has collected detailed information on multiple potential confounding factors which were included in analyses, unlike the main analyses of the Collaboration[7] which were only adjusted for age, study or study centre and measures of sexual behaviour.

Although the analyses presented here represent the largest single prospective study of which I am aware, this cohort being from the UK is still relatively underpowered for extreme categories of parity or age at first FTP, particularly by histotype. As such, with wide confidence intervals in some categories in these analyses, it is possible that some real associations were missed in this investigation.

Another important limitation is the lack of measures of sexual behaviour and information on HPV status in this study which means potential confounding by

these factors cannot be fully ruled out. However as discussed in **Section 6.3.4.3**, age at first FTP, adjusted for in my analyses, is likely to be a good proxy for age at first sexual intercourse in study populations where the latency between first sexual intercourse and first pregnancy is likely to be short e.g. in older women as in the MWS.[247] The Collaboration has also noted previously that in this case i.e., when age at first intercourse is shortly followed by age at first FTP, controlling for either factor when examining the effect of the other may result in overadjustment, potentially introducing new bias to analysis.[74]

The lack of information on HPV status of the women in this cohort is another potential limitation. However, the Collaboration found that although results in analyses restricted to HrHPV positive cases and controls were of a stronger magnitude, they were largely similar to the main analyses i.e., the same conclusions concerning the direction and statistical significance. Furthermore, while we do not have a measure of HPV status in MWS data, past screen-detected abnormalities, which have been included as an adjustment in all analyses, are likely to be a marker of HPV infection.[231, 248] In a large meta-analysis looking at HPV across different grades of cervical abnormalities, HPV prevalence increased with increasing severity of abnormality, from 12.6% in normal cytology to 85% in high-grade lesions.[248] HPV types classified as probably carcinogenic (high risk types) were also more commonly found in more severe disease. It therefore expected that adjusting for previous screening test results should go some way toward adjusting for HPV status.

6.4 Conclusion

The current study supports with prospective evidence previous conclusions on an independent effect of early age at FTP on incident pre-invasive and invasive cervical cancer. Multiparity was also independently associated with the risk of CIN3 but there was no clear evidence that multiparity was associated with the risk of ICC after adjustment for age at FTP. This study has also shown that, when compared to nulliparous women, risk estimates for ICC associated with multiparity and early

age at first FTP are substantially strengthened with adjustment for past cervical screening history, with the strongest effects found for squamous cell carcinoma.

6.5 Tables

Search strategy	
(#1)	((((((cervical neoplasm, uterine[MeSH Terms]) OR (uterine cervical neoplasm[MeSH Terms])) OR (cervical intraepithelial neoplasia, grade iii[MeSH Terms])) OR (cancers, squamous cell[MeSH Terms])) OR (carcinoma, squamous cell[MeSH Terms])) OR (adenocarcinoma[MeSH Terms]))
(#2)	((((((parity[MeSH Terms]) OR (birth of full term newborn[MeSH Terms])) OR (birth[MeSH Terms])) OR (reproductive risk)) OR (age at first birth)) OR (reproductive factors))
((#1) AND (#2))Filters: from 2006 - 2021	

Table 6.1: Search strategy

Study design	Publication (Region)	Confounding				Total Cases/Population	Parity	RR(95% CI)	Number of FTPs				Age at first FTP, years			
		Screening	Sexual behaviour	HPV	Other				All women	RR(95% CI)*	Parous women	RR(95% CI)	All women	RR(95% CI)	Parous women	RR(95% CI)
IPD meta-analysis	The Collaboration, 2006[7] (Various[a])	Yes; ever vs. never screened[b]	Yes; AFSI and number of lifetime partners	No	Age and study or study centre	11,161/44,703			Nulliparous	1.00 (ref)	Parous, 1-2	1.00 (ref)	Nulliparous	1.00 (ref)	25+	1.00 (ref)
									...	...	...	...	...	...	...	...
									7+	2.39 (2.03-2.81)	7+	1.76 (1.53-2.02)	<16	2.62 (2.16-3.17)[c]	<17	1.77 (1.42-2.23)
										Trend: p<0.001		Trend: p<0.001		Trend: p<0.001		Trend: p<0.001
Prospective studies	Roura *et al.*, 2016[11] (Europe[d])	No	No	No	BMI, marital status, education, physical activity, smoking habits, OC use and duration and menopausal status and MHT use	261/308036	Nulliparous	1.00 (ref)	Nulliparous	1.00 (ref)					30+	1.00 (ref)
							Parous	0.7 (0.5-1.0)	...	...					...	...
									4+	0.9 (0.5-1.6)					≤ 20	1.1 (0.6-2.0)
										Trend: p=0.4						Trend: p=0.8
	Paltiel *et al.*, 2016[236] (Israel)	No	No	No	Age at first birth, ethnic origin, education	74/27,949					Parous, 1-4	1.00 (ref)				
											5+	0.77 (0.45-1.34)				
	Thulaseedharan *et al.*, 2012[237] (India)	No	Yes; age at marriage	No	Household income, age, formal education, occupation	158/30,958			Nulliparous	1.00 (ref)						
									...	...						
									4+	7.1 (1.0-51.8)						
										Trend: p=0.002						
Retrospective	Singini *et al.*, 2021[238] (South Africa)	No	No	No	Age, education, marital status,period of the interview,residence	3450/9159					Parous, 1-2	1.00 (ref)				
											3+	OR 1.25 (1.07-1.46)				
												Trend: p=0.002				
	Pasdar *et al.*, 2021[239] (Scotland)	No	No	No	Height and age at first delivery	152/304					Parous, 1	1.00 (ref)			<20	1.00 (ref)
											2	OR 1.04 (0.60-1.81)			21-25	OR 0.23 (0.12-0.46)
											3+	OR 1.37 (0.73-2.56)			26-30	OR 0.37 (0.16-0.86)
	Thakur *et al.*, 2015[240] (India)	No	Yes; age at marriage	No	Illiteracy, age at first birth, pregnancy spacing,genital hygiene, SES	226/452					Parous, <3	1.00 (ref)			<19	1.00 (ref)
											3+	OR 1.70 (1.26-2.65)			19+	OR 0.34 (0.28-0.54)

Table 6.2: Characteristics and results of studies included on the risk of invasive cervical cancer in relation to reproductive factors, parity and age at first full-term pregnancy (FTP)

Abbreviations: AFSI, age at first sexual intercourse; BMI, body mass index, OC, oral contraceptive; MHT, menopausal hormone therapy; SES, socioeconomic status

[a] United Kingdom, Norway, Sweden, USA, Denmark,Costa Rica, Colombia, Spain, Chile, Australia, Israel, Mexico, Thailand, Italy, Panama, Paraguay Brazil, Mali, Philippines, Morocco, Peru, Algeria, India, South Africa, Kenya, Nigeria

[b] Adjusted for likelihood of screening based on self report or knowledge of availability of screening in each country

[c] Floated confidence interval reported

[d] France, Germany, Greece, Italy, the Netherlands, Spain, Denmark, Norway, Sweden and the United Kingdom

Study design	Publication (Region)	Confounding				Total Cases/Population	Parity	RR(95% CI)	Number of FTPs				Age at first FTP, years			
		Screening	Sexual behaviour	HPV	Other				All women	RR(95% CI)*	Parous women	RR(95% CI)	All women	RR(95% CI)	Parous women	RR(95% CI)
IPD meta-analysis	The Collaboration, 2006[7] (Various) [a]	Yes; ever vs. never screened[b]	Yes; AFSI and number of life-time partners	No	Age and study or study centre	5402/38,944			Nulliparous	1.00 (ref)	Parous, 1-2	1.00 (ref)	Nulliparous	1.00 (ref)	25+	1.00 (ref)
	Outcome: CIN3/CIS								...	...	...	...	...	...	...	...
									7+	1.60 (1.30-1.98)	7+	1.15 (0.92-1.44)[c]	<17	2.06 (1.63-2.59)[c]	<17	1.78 (1.26-2.51)
										Trend: p<0.001		Trend: p=0.27	Trend: p<0.001		Trend: p<0.001	
Prospective studies	Roura *et al.*, 2016[11] (Europe[d])	No	No	No	BMI, marital status, education, physical activity, smoking habits, OC use and duration and menopausal status and MHT use	804/308036	Nulliparous	1.00 (ref)	Nulliparous	1.00 (ref)					30+	1.00 (ref)
	Outcome: CIN3/CIS						Parous	1.5 (1.2-1.9)	...	...					...	...
									4+	2.3 (1.6-3.3)					≤ 20	1.2 (0.9-1.7)
										Trend: p=0.03						Trend: p=0.2
	Jensen *et al.*, 2013[235] (Denmark)	No	No	Yes	Smoking status and length of schooling	241/1353	Nulliparous	1.00 (ref)	Nulliparous	1.00 (ref)						
	Outcome: CIN3+ [e]						Parous	1.39 (1.02-1.91)	1	1.33 (0.94-1.90)						
									2+	1.58 (0.91-2.71)						

Table 6.3: Characteristics and results of studies included on the risk of cervical intraepithelial neoplasia, grade 3 (CIN3) in relation to reproductive factors, parity and age at first full-term pregnancy (FTP)

Abbreviations: AFSI, age at first sexual intercourse; BMI, body mass index, OC, oral contraceptive; MHT, menopausal hormone therapy; SES, socioeconomic status

[a] United Kingdom, Norway, Sweden, USA, Denmark,Costa Rica, Colombia, Spain, Chile, Australia, Israel, Mexico, Thailand, Italy, Panama, Paraguay Brazil, Mali, Philippines, Morocco, Peru, Algeria, India, South Africa, Kenya, Nigeria

[b] Adjusted for likelihood of screening based on self report or knowledge of availability of screening in each country

[c] Floated confidence interval reported

[d] France, Germany, Greece, Italy, the Netherlands, Spain, Denmark, Norway, Sweden and the United Kingdom

[e] CIN3+ was defined as histologically diagnosed severe dysplasia and carcinoma *in situ*; or similar cytological diagnoses without histological confirmation

	% (n) of women*	
	Parous	**Nulliparous**
Mean age at baseline (SD)	56.1 (4.4)	56.1 (4.5)
Most deprived tertile	33 (253 612)	32 (31 724)
No educational qualifications	44 (333 799)	34 (33 037)
Body mass index 30+ kg/m^2	17 (125 050)	16 (14 969)
Current smokers	20 (150 042)	17 (16 501)
Ever oral contraceptive use	62 (475 709)	47 (46 366)
Ever menopausal hormone therapy use	44 (337 636)	41 (40 089)
No screening test record	2 (12 636)	12 (11 488)

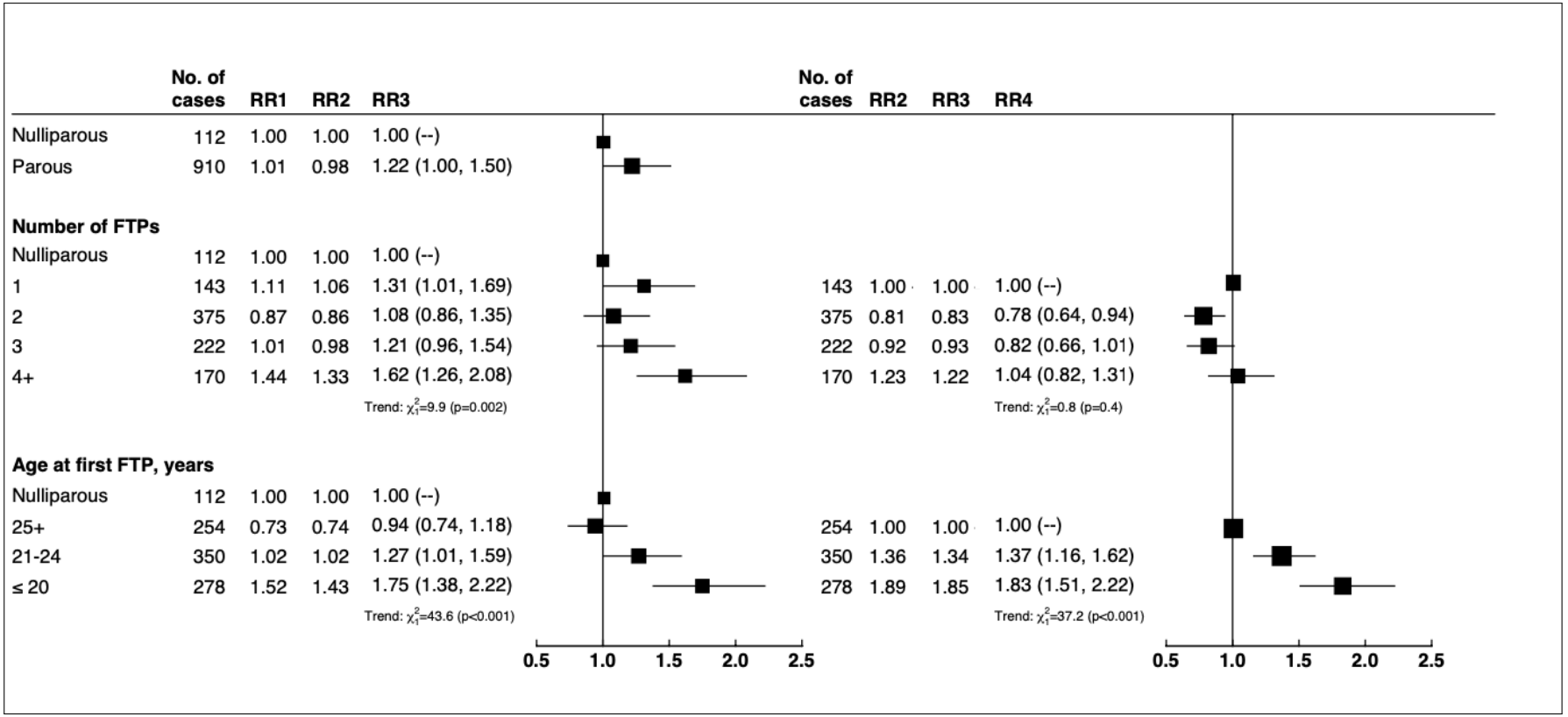
Table 6.4: Recruitment characteristics of women included in analyses of risk of ICC analyses according to parity

* unless otherwise indicated

Estimates calculated in women with no missing values

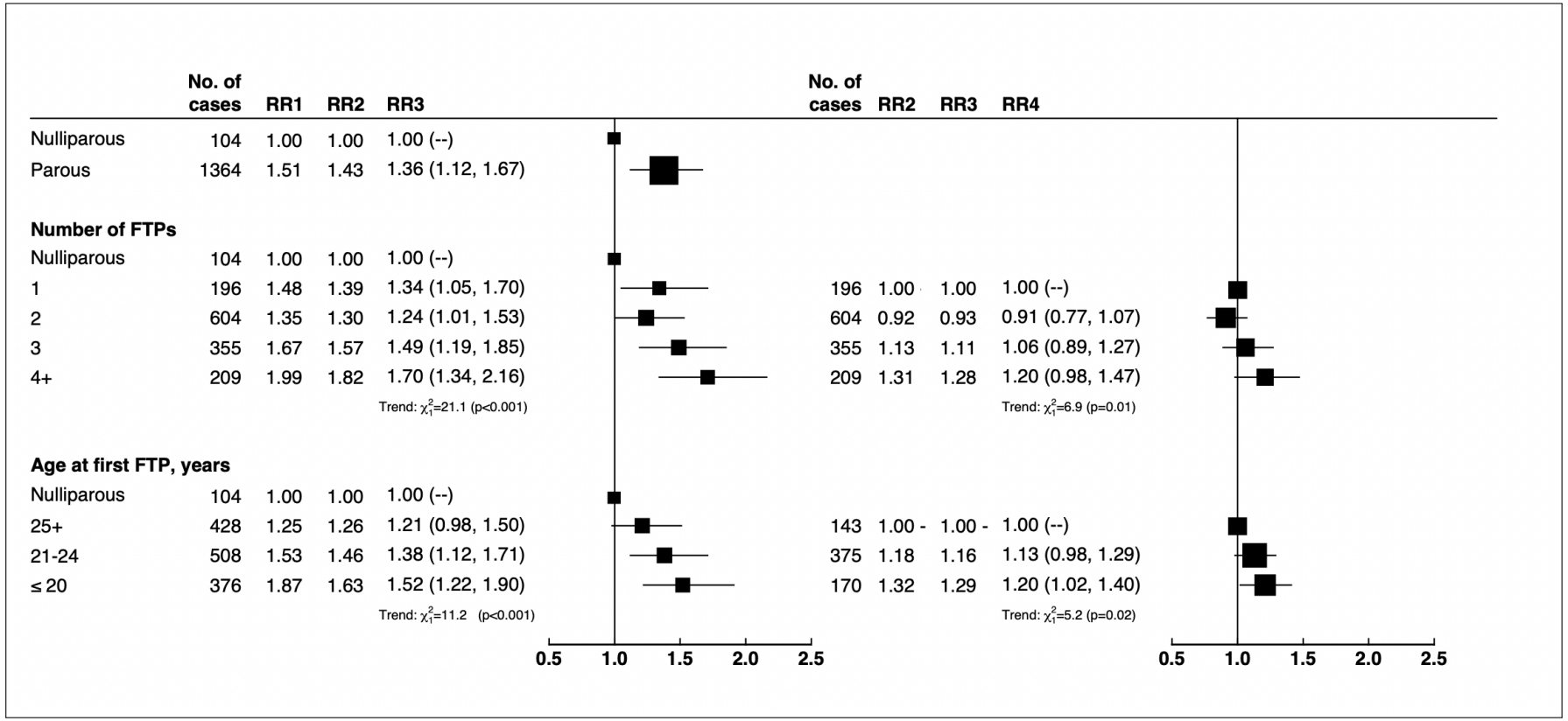
6.6 Figures

Figure 6.1: Relative risks (RR) and 95% confidence intervals (CI) of invasive cervical cancer in relation to reproductive factors: number of full-term pregnancies and age at first full-term pregnancy (FTP)



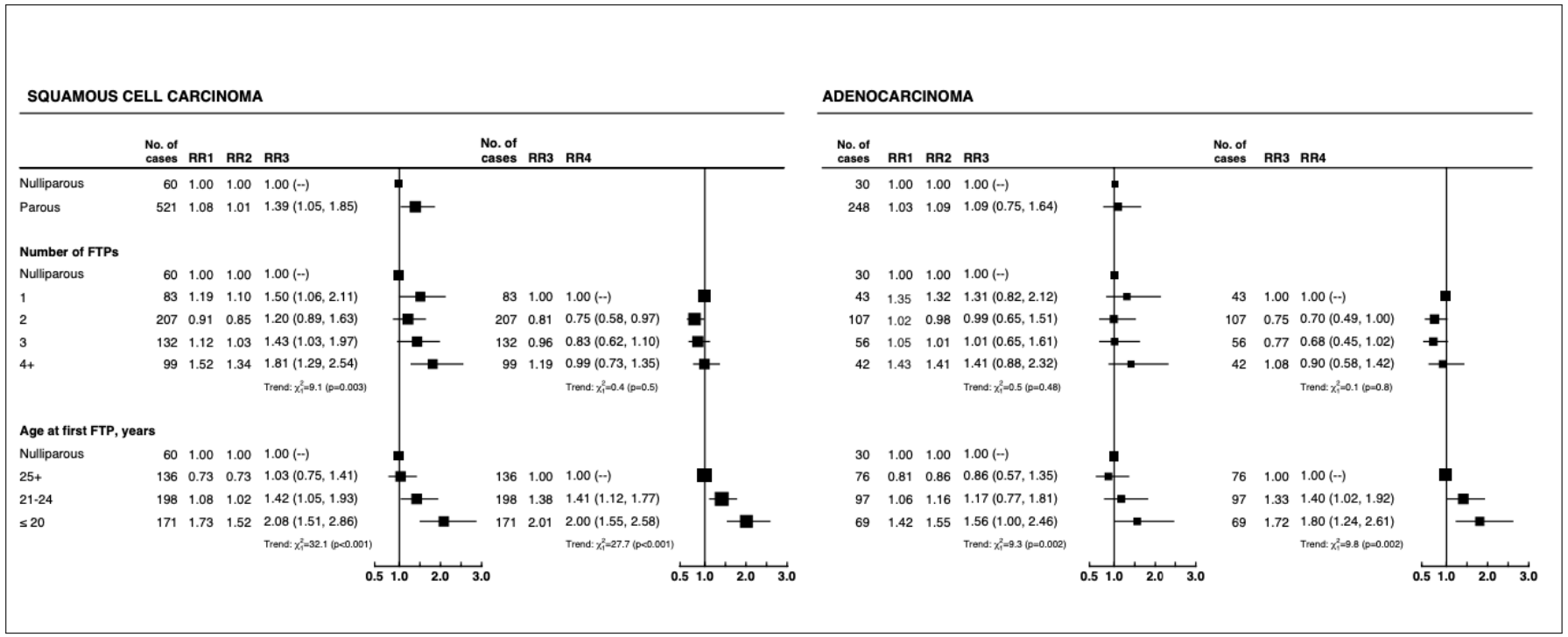
RR1, relative risk adjusted only for region of recruitment and deprivation tertiles; **RR2**, relative risk adjusted for region of recruitment deprivation tertiles,education, smoking status, body mass index, menopausal hormone and oral contraceptive use; **RR3**, relative risk as in RR2 and additionally adjusted for screening history; **RR4** relative risk as in RR3 and additionally adjusted for age at first FTP or number of FTPs as appropriate

Figure 6.2: Relative risks (RR) and 95% confidence intervals (CI) of cervical intraepithelial neoplasia grade 3 (CIN3) in relation to reproductive factors: number of full-term pregnancies and age at first full-term pregnancy (FTP)



RR1, relative risk adjusted only for region of recruitment and deprivation tertiles; **RR2**, relative risk adjusted for region of recruitment deprivation tertiles,education, smoking status, body mass index, menopausal hormone and oral contraceptive use; **RR3**, relative risk as in RR2 and additionally adjusted for screening history; **RR4** relative risk as in RR3 and additionally adjusted for age at first FTP or number of FTPs as appropriate

Figure 6.3: Relative risks (RR) and 95% confidence intervals (CI) of squamous cell and adenocarcinoma of the cervix in relation to reproductive factors; number of full-term pregnancies and age at first full-term pregnancy (FTP)



RR1, relative risk adjusted only for region of recruitment and deprivation tertiles; **RR2**, relative risk adjusted for region of recruitment deprivation tertiles,education, smoking status, body mass index,menopausal hormone and oral contraceptive use; **RR3**, relative risk as in RR2 and additionally adjusted for screening history; **RR4** relative risk as in RR3 and additionally adjusted for age at first FTP or number of FTPs as appropriate

There's no good answer to being a woman; the art may instead lie in how we refuse the question

— Jia Tolentino

7

Oral contraceptives and the risk of cervical neoplasia

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7.1 Introduction

Worldwide, more than 150 million women — an estimated 15% of all women of reproductive age — currently use oral contraceptives (OC). [249] The International Agency for Research on Cancer (IARC) has classified OCs as carcinogenic to humans based, in part, on an evaluation of observational evidence which concluded that there is sufficient evidence of an increased risk of invasive cervical cancer (ICC)in current and recent OC users, with no variation in risk by cervical tumour histotype.[6, 8, 250] Risks associated with OC use were also found to be somewhat greater for carcinoma *in situ* (CIS) including cervical intraepithelial neoplasia grade 3 (CIN3).[250] However, previous observational evidence is largely retrospective, which has been recognised as misleading in the studies examining the risk of reproductive cancers associated with exogenous hormone use.[251, 252] Another problem in interpreting previous evidence on observed associations between cervical cancer and contraceptive use has been the limited ability to take account of the possible effect of selective cervical screening attendance.

In this chapter, I present the findings of a narrative review of previous evidence on OC use and the incidence of cervical neoplasia i.e., CIN3 and overall ICC, including separately by major histo-type, squamous cell carcinoma (SCC) and adenocarcinoma (AC). I then report on a detailed investigation of these relationships in the Million Women Study (MWS) which has prospectively collected information on OC use and almost two decades of follow-up. Specifically, this investigation 1) evaluates the association between different measures of OC use and risk of CIN3 and ICC overall; 2) examines the relationship between OC use and ICC risk by tumour subtypes; and 3) investigates the effect of adjustment for screening history, as defined in **Chapter 5**, on risk estimates of cervical neoplasia in relation to OC use.

7.2 Literature Review

7.2.1 Objectives

The aim of this review is to summarise previous evidence on OC use and incidence of cervical neoplasia, including high-grade precursor lesions (CIN3), overall ICC and major subtypes of ICC, SCC and AC, where possible.

7.2.2 Methods

To summarise what is known on the risk of cervical neoplasia associated with OC use, I first summarise the findings of two individual participant data meta-analyses underlying current perspectives on this relationship published by the International Collaboration of Epidemiological Studies of Cervical Cancers ("the Collaboration"). The first reports on an investigation of the risk of CIN3 and overall ICC associated with OC use,[6] and the second explored potential variation in associations with OC use by invasive cancer histo-type.[8] I then present the findings of a literature search of online database PubMed for all subsequently published evidence on OC use in relation to the incidence of all ICC and CIN3 [November 2007 to 1 June 2022] and separately by histo-type [March 2007 to 1 June 2022]. Search strategy is summarised in **Table 7.1**.

Any original observational studies (retrospective or prospective) published in peer-reviewed journals examining the association between hormonal contraceptive (HC) use and the risk of cervical neoplasia were included. In many studies the term hormonal contraceptive is used irrespective of form, as such, any HC use was included since many users of HC use combined oral contraceptive pills. [249] Studies were defined as "retrospective" if information on HC use was recorded after CIN3/ICC diagnosis. Only studies with an outcome of ICC (or histo-types SCC or AC) and CIN3 or CIN3/CIS were included, with the exception of Xu *et al.* who included CIN2/3.[253] Studies on recurrence and/or progression of disease were not included in this review. The minimum study size for case-control studies was at least 100 cases of ICC or at least 200 cases of CIN3/CIS and at least 30

cases for cohort studies. These criteria were defined to be similar to those used to select studies for both meta-analyses.[6, 8].

Details on study characteristics including study size, region, adjustment for relevant confounding including screening history, sexual behaviour and measure of human papillomavirus (HPV) status were extracted. Maximally adjusted measures of risk of all outcomes associated with duration of use, time since last use and/or a combination of duration and time since last use of HCs were extracted from each article and are presented.

7.2.3 Results

A total of seven eligible studies were identified on the association between HC use and the risk of cervical neoplasia. Study characteristics and results are presented in text and in **Tables 7.2 - 7.4**.

7.2.3.1 Risk of ICC

Based on 11,170 cases with 35,509 controls, the Collaboration found that the risk of ICC increased with increasing duration of use of OCs (trend: $p<0.0001$), and declined after use ceased (trend: $p<0.0001$).[6] Women who had used OCs more recently had also, on average, used them for a longer duration whereas women who had last used OCs less recently had used them for a shorter duration on average. For short-term users (<5 years, mean 2.9 years), there was no significant increase in risk of ICC in any category of time since last use, but for women with longer durations of use (5+ years, mean 9.8 years) the RR of ICC in current users was almost double that of never users and significantly declined with increasing time since last use (RRs [95% CI]: 1.90 [1.69-2.13] and 0.94 [0.80-1.08] for current and 10+ years since last use vs. never users respectively, trend: $p<0.0001$). (**Table 7.2**). In analyses stratified by study design, no trend across time since last use was reported and for prospective studies the RRs [95% CI] per year of use were 1.03 [0.97-1.09] and 1.01 [0.98-1.04] for current use and 10+ years since last use respectively (data not shown in **Table 7.2**). Significant heterogeneity was, however, noted by study design (i.e.,

between prospective and retrospective studies) for the least recent group of of OC users (who formed the bulk of prospective cases [55% of cases]).

The Collaboration explored the following potential confounding: screening history, HPV status and sexual behaviour.[6] For screening history, women were classified by whether or not they were likely to have ever had a Pap smear, and where this was not possible, screening history was assigned based on the knowledge of availability of screening in the country of residence. Analyses stratified by screening history, defined in this way, showed no material differences in patterns of risk between women likely to have ever vs. never been screened. In a sensitivity analysis in women for whom data for all adjustment variables were available, adjustment for screening was associated with a 10% fall in the χ^2 value for OC use, which provides a measure of the extent of confounding. Information on HPV status was available for about half of the studies (13 of 24 studies), and the pattern of risks associated with OC use was similar to that seen for all women in analyses restricted to these studies. The risk pattern was also similar when analyses were restricted to high-risk HPV-positive women only (88% of cases) in these studies. Finally, while all analyses adjusted for sexual behaviour variables, age at first sexual intercourse (AFSI) and lifetime number of sexual partners, effects of adjustment were only reported in the sensitivity analysis in women for whom data for all adjustment variables were available. Adjustment for these variables had the largest effects of all potential confounders included on relative risk estimates for ICC (40% and 30% fall in the χ^2 value for OC use for AFSI and lifetime number of sexual partners respectively).

Since the meta-analysis, six studies[11, 254–258] (4 prospective, 2 retrospective) have subsequently published findings on the risk of ICC in relation to use of HCs. (**Table 7.2**) The first publication was a report from the Oxford Family Planning Association (FPA) Oral Contraceptive Study which included 17,032 women aged 25–39 years who were recruited in the late 1960s. The study was closed in 2010, publishing this final report of results in 2013.[255] Data from this study was previously included in the meta-analysis (42 cases), although by the final report, it had accrued an additional 19 cases. After 628,000 woman years of follow-up, similar

to the meta-analysis, they found that short term-use of OCs (<73 months) was not associated with a significant increase in risk of OC, regardless of interval since last use. A significantly increased risk was seen for longer users (73+ months) in all categories of interval since last use with apparent decline in successive categories, although a test for trend was not reported. Unlike the meta-analysis, however, the excess risk seen in users of longer duration persisted for longer (RRs for users of 73+ months, [95% CI]: 5.3, [2.2-15.0]; 4.3, [1.5-13.1] and 3.2, 95% CI: 1.0-10.2 for <48, 49-144, 145+ months since last use respectively). (**Table 7.2**) No information on screening history or HPV status was available for adjustment in this study. An adjustment for age at first marriage was included as a proxy for sexual behaviour and was reported to have a statistically significant effect on the age-adjusted RR.

Results from the European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort, which aimed to contribute prospective evidence on the role of hormones including OC use on the risk of ICC, were published in 2016.[11] After a median of 9 years of follow-up, 261 cases of ICC were diagnosed in the cohort of 308,036 women recruited between 1992 and 2000. In contrast to the meta-analysis, no significant trend was seen with increasing duration of use in ever users (trend: p=0.2) or time since last use in past users (trend: p=0.7). They reported no pattern of risk when the combined effect of duration and recency of OC use was evaluated for ICC, although no data were given. Findings on duration of use were broadly similar, although attenuated, in a nested case-control study which adjusted for HPV serological markers and in analysis restricted to all cases and HPV positive controls. However, there were not enough cases of ICC to assess recency of use in the case-control analysis. No information was available on sexual behaviour or screening history.

Data from the next prospective study, the Royal College of General Practitioners (RCGP) Oral Contraception Study, was also included in the meta-analysis (162 cases in meta-analysis).[256] This study recruited in 1968-1969 and in the latter article, published in 2017, reported the effects of past OC use on the life-time risks of cancer with additional follow-up to 2012 and 30 additional cases.[256] The

conclusions were broadly similar to the meta-analysis as shown in **Table 7.2**. After 44 years of follow-up of 46,022 women, among ever users of OCs (mean duration of use, 3.7 years) the increased risk of ICC seen in current or recent users (<5years) at recruitment declined to that of never users within about 5 years of stopping use and did not reappear in later life (IRRs, [95% CI]: 2.32, [1.24-4.34]; 1.52, [0.84-2.75] and 0.51, [0.16-1.67] for current/recent use; 5-15 years and 35+ years since last use compared to never users). There was no information available on screening history, HPV status or sexual behaviour in this study.

The most recently published article, based on a prospective study of women living in Denmark from 1995 to 2014 (n=1 853 542) aimed to determine the risk of ICC associated with contemporary HCs (containing lower oestrogen concentrations of <35μg).[254] Similar to the meta-analysis, the risk of ICC in ever users (mean duration of use, 5.9 years) was increased with increasing duration of use (trend: p<0.001) and decreased with increasing time since last use(trend: p<0.001). For women with 5 or more years of use, the risk in recent users (>1-<5 years) was RR: 1.55, 95%CI: 1.27-1.89. The increased risk appeared to decline after use ceased, and by 10 or more years there was no significant increase in the relative risk of ICC compared with never users (RR:1.29, 95% CI: 0.65-2.56), although no test for trend was reported. There was no information available on screening history, HPV status or sexual behaviour in this study.

Findings from two retrospective studies have been published since the meta-analysis, with broadly similar findings.[257, 258] (**see Table 7.2**) Based on 2,182 cases and 1,492 controls, the first study,[257] reported on risks associated with the use of oral or injectable contraceptives in Johannesburg, where the use of injectable contraceptives is more common than use of OCs.[259] Data from this study was also included by the Collaboration, however, there were over 1000 additional cases in the more recent publication. Adjusting for lifetime number of sexual partners, they found that longer use of OCs (5+ years) was associated with an increased risk of ICC in more recent users (<10 years since last use) but not in less recent users (10+ years since last use) (ORs, [95% CI]: 1.37 [1.05-1.78] and 1.00 [0.78-1.27]

respectively). Information on screening history was missing for 61% of participants and this variable was not included in main analyses. However, no material differences in ORs were noted in sensitivity analysis after multiple imputation of the missing screening histories. No information on HPV status was available in this study.

Finally, in a smaller Iranian study of 300 cases and an similar number of controls (319 controls), after adjusting for potential confounders, there was no significant association seen with ICC for increasing duration of OC use (OR, 1.04 95% CI:0.98-1.1 per year of use).[258] However, there was an increased risk of ICC for more recent users of OC (OR, 1.4 95% CI:1.01-2.1 for <8 years vs 8+ years since last use). Potential confounders included age at first marriage, age at first birth and multiple marriages as proxies for sexual behaviour, which were reported as having significant effects in the minimally adjusted models. No information on HPV status or screening history was available.(see **Table 7.2**)

7.2.3.2 Risk of CIN3

In the 2007 meta-analysis, from a total of 5,403 cases, it was reported that the risk of CIN3/CIS in current users was increased with increasing duration of use of OCs.[6] For women who had used OCs for 5 or more years the relative risk of CIN3/CIS in current users was 2.23, 95% CI: 1.99-2.47 and significantly declined ($p<0.001$) with increasing time since last use (RR: 1.35, 95% CI: 1.13-1.57 for 10+ years since last use) compared to never users.[6]. The effects of adjustment for sexual behaviour variables, screening history and restriction to HPV positive women, were not reported for analyses specific to CIN3/CIS.

Two published studies (1 prospective, 1 retrospective) have since reported on the association between HC use and high-grade precursor lesions (specifically CIN3/CIS[11] and CIN2/3[253]). The first study,[11] based in the EPIC cohort described in **Section 7.2.3.1** above, found an increased risk of CIN3/CIS for increasing years of use of OCs in ever users (RRs, [95% CI]: 1.0, [0.8-1.3] to RR: 1.6, [1.2-2.2] in users $\leq$ 1 year to 15+ years of use respectively, trend: p=0.01). There was no significant trend for recency of use (trend: p=0.2).(**Table 7.3**) In

analyses for the joint effect of duration and recency for the risk of CIN3/CIS they reported that the “risk declined with increasing time since last use" although data were not given and it is unclear what categories of duration or time since last use were included in these analyses. As with ICC, no information on screening or sexual behaviour was available and associations were broadly similar, but attenuated, in the nested case-control analysis adjusted for HPV serological markers and in analysis restricted to all cases and HPV positive controls.

The second study was an Australian retrospective study which reported findings based on 886 cases with CIN 2/3 and 3636 controls recruited from a screening registry with the aim of contributing to the Australian-specific literature on the risks of ICC associated with HC use.[253] For women with longer durations of use (15+ years), the risk in current users was almost double that of never users whilst current users of shorter duration had no significant risk of CIN2/3 (RRs [95%CI] 1.82 [1.22-2.72] 1.22-2.72) and 1.13 [0.75-1.75] for current users of 15+ and <10 years duration respectively, trend:p=0.04). By contrast, the risks for past users did not vary significantly according to duration of use (p=0.75) (see **Table 7.3**). Results were reported to have remained largely unchanged after adjustment for sexual behaviour variables: number of sexual partners and age at first sexual intercourse. Analyses were also adjusted for the number of Pap smears in the 5 years preceding the index date, however the effect of adjustment was not reported. No information on HPV status was available.

7.2.3.3 Histological subtypes

The Collaboration, which included 1,581 women with SCC, 321 women with AC (including adenosquamous carcinoma) and 4,827 controls, found that current users of combined OCs had a higher risk of both SCC and AC (RR per year of use: 1.08, 95% CI: 1.06-1.09 and 1.07, 95% CI: 1.04-1.11 for SCC and AC respectively) that significantly waned (trend: $p< 0.001$) with increasing time since last use (RR per year of use: 0.98, 95% CI: 0.96-1.00 and 1.02, 95% CI: 0.97-1.07 for SCC and AC respectively for 10+ years since stopping). However, there were

no significant differences between squamous cell and adenocarcinoma for these associations (case-case comparison, heterogeneity: p=0.1). (see **Table 7.4**). The effect of adjustment for screening history, sexual behaviour or HPV status on the risk of SCC/AC associated was not reported.

To my knowledge, only two prospective studies have reported on the risk of SCC and AC associated with HC use since the meta-analysis.[11, 254] First, based on 2,720 SCC and 626 AC cases with a mean duration of use of 5.8 years in ever users, Iversen *et al.*[254] found that current or recent use (within 1 year of stopping) of any contemporary HC (<35μg oestrogen) was significantly associated with an increased risk of both SCC and AC compared to never use (RR: 1.31, 95% CI: 1.19-1.44 and RR: 1.29, 95% CI: 1.05-1.60 for SCC and AC respectively), although no formal test between the two was reported. The EPIC cohort, [11] also reported an increased risk of SCC in ever users with increasing years of OC use, although “non-significant weak positive associations" for AC were reported and data for this analysis was not presented.[11]

7.2.4 Discussion

In their summary of worldwide evidence, The Collaboration reported that the risk of ICC increased significantly with increasing duration of use and declined with increasing time since last use. However, these variables were also demonstrated to be highly inter-related and in a combined analysis of these timing variables, there were no significant effects for users of shorter durations (<5 years) regardless of recency of use, however, for users of longer durations (5+ years), there was an increased risk of ICC in current users that declined to that of never users by 10 years since last use. A similar pattern of risk was seen in the meta-analyses for CIN3/CIS, although somewhat stronger in longer users of OCs, with persistent increased risks 10 or more years since last use.[6] The equivalent results in studies restricted to women positive for HPV, and in women positive for high-risk HPV were consistent with the results for all women. The relative risks for OCs per year of use were about 10% lower with adjustment for screening but the largest

effect was found when estimates were adjusted for AFSI (around 40%). When comparing histotypes, the Collaboration found no evidence of heterogeneity in risk associated with OC use between SCC and AC.[8]

The findings in subsequently published evidence on risk of ICC have been broadly similar: for women who had used OCs for longer durations, there was evidence that women with most recent use (and potentially longer durations of use) had significantly increased risk of ICC.[254, 255, 257] This risk declined with increasing time since last use (and potentially shorter duration of use) reaching that of never users after about 10 years in all studies except the Oxford FPA where an effect was still present 12 or more years after cessation of use. Significant trends with longer durations of use in more recent users have also been reported for high-grade precursor lesions (including CIN3) in more recent evidence.[253] Since the Collaboration's 2007 publication, only two studies have explored associations with OC use stratified by histotype although neither formally tested for heterogeneity by histo-type.[11, 254] Only one study published since the meta-analysis has had information on HPV status,[11] and results from these analyses were broadly similar to main analyses, although attenuated after adjustment for HPV status and restriction to HPV positive women. With respect to sexual behaviour, only two studies have had information for adjustment: Xu *et al.,* who reported that results remained consistent after adjustment for sexual history (AFSI and number of partners) and Urban *et al.,* who did not report effects of adjustment. A single study had information on screening history, but did not report effects of adjustment.[253]

While these studies have provided important information on the risk of cervical neoplasia associated with use of OCs, they are largely driven by retrospective evidence, with only 4% of the total number of ICC cases and <0.5% of cases for both histo-types in the Collaboration meta-analyses coming from prospective studies. In retrospective studies, information on contraceptive use is recorded after the disease is diagnosed and therefore prone to recall bias, particularly in cases whose recollection may be changed by their cancer diagnosis. Users of OCs may also have been more willing to participate as controls. In studies of risks associated

with hormone use in other reproductive cancers, such as ovarian and breast cancer, retrospective studies have been shown to give rise to different results when compared to results from prospective studies.[251, 252] For example, in a recent meta-analysis of breast cancer risk associated with use of menopausal hormone therapy (MHT), the RRs for duration of use of MHT were about one-fifth lower in the retrospective than in the prospective studies.[252] This difference was partly attributed to difficulties in selection of controls in many of the retrospective studies, but also to the relatively shorter durations of use of MHT reported in many of the retrospective studies. Given this potential for heterogeneity the Collaboration has reported results in their 2007 meta-analysis on OCs separately for prospective and retrospective studies, and subdivided the latter by studies that used population controls versus hospital controls; and for users of OC who had last used them 10 or more years previously there were some differences by study design.[6]

The lack of adequate data on previous cervical screening tests also makes interpretation of previous findings challenging. In the Collaboration meta-analyses, women were classified only by whether or not they were likely to have been previously screened based largely on self-reported screening status. However, in studies where individual screening information was not available (including two large cohort studies- the MWS and the Oxford FPA Study- contributing 50% of prospective ICC cases) screening history was determined based on the knowledge of availability of screening in the study region. Since the Collaboration publications, as mentioned, only one study has included an adjustment for screening in their main analysis of the risk cervical neoplasia associated with OC use;[253] and one other reported adjustment for number of Pap smears in a sensitivity analysis of multiply imputed data (61% missing).[257] No other studies report any adjustment and the lack of screening data is acknowledged as a limitation by the authors.[11, 254] Given that users of OCs may be more likely to attend for cervical screening than non-users (see **Table 4.6, Chapter 4**), the risks of ICC associated with OC use may have been underestimated. This is because women who attend for screening would have precursor lesions such as CIN3 detected and treated before progression to invasion to

cancer. Similarly, the risks of CIN3 associated with OC may have been overestimated i.e., detection bias. This is particularly a concern outside of organised programmes, where users of OCs may have had more opportunistic screens taken than non-users. In the meta-analysis,[6] majority of the studies (18 of 24 studies) came from either countries without organised programmes, or where cases were diagnosed before the organised screening programmes were established making the interpretation of findings potentially complicated in women who have been previously screened.

Finally, since the Collaboration's meta-analysis comparing histo-type, published evidence on the risk of ICC associated with OC use by histo-type has remained limited[11, 254] and, to my knowledge, has not formally tested for heterogeneity in these associations. The Collaboration was also not able to distinguish between AC and rarer histo-types, namely adenosquamous carcinoma, which have been suggested to behave differently from AC.[8, 190, 260] Adenocarcinomas consitute approx. 20% of all cervical cancers in most populations and a relative and absolute increase in the incidence of AC has been reported.[97, 261] There is therefore need for reliable research on the aetiology of these cancers.

Reliable prospective assessment of the association of OC use and incident CIN3 and ICC, taking into account a potential confounding effect of screening, is needed. Further clarification on associations between OC use and risk of cervical cancer by histo-type in prospective analysis is also warranted.

7.3 Oral contraceptive use and the risk of cervical neoplasia

7.3.1 Objectives

The analysis that follows will examine the risk of ICC, CIN3, SCC and AC in relation to OC use, taking account of screening history as defined in previous chapters.

7.3.2 Methods

7.3.2.1 Study cohort

Data were obtained from the MWS with linked NHSCSP records. The methods of recruitment, data collection, follow-up, and ascertainment of cervical cancer for the MWS; and extraction and linkage with NHSCSP screening data have been described in detail in **Chapter 3**.

Of the 874,175 women eligible for inclusion for the analyses of the risk of ICC and 843,389 for the risk of CIN3 (see **Chapter 3 Section 3.6.1**), 8,355 women with missing information on OC use were also excluded in analyses for the risk of ICC and 8,320 for analyses for the risk of CIN3.

7.3.2.2 Exposure variables

The questions used to assess OC use in this cohort have been described in **Chapter 3**.

Analyses examined the following OC exposures relative to never use based on the recruitment questionnaire: ever use; duration of use (<5, 5-9, 10+ years); and time since last use in past users which was treated as a time dependent variable and assumed to increment by 1 year annually until the end of follow-up (<25,25-35,35+ years for ICC; never and <20,20-25,25-30,30+ years for CIN3). Considering the high correlation between duration and time since last use previously reported,[6] I also examined a cross-classification of these variables. I examined duration per year of use within categories of time since last use (<25/25+ years for CIN3 and <30/30+ years for ICC) due to insufficient numbers to examine a categorical duration variable.

7.3.2.3 Outcomes

The main outcomes of interest were cervical intraepithelial neoplasia, grade 3 [CIN3] (International Classification of Diseases 10th Edition [ICD-10] code D06) and invasive cervical cancer (ICD-10 code C53). For analyses of histotype, the outcome was split into the two most common histological groups: squamous cell carcinoma and adenocarcinoma by combining ICD-10 codes with ICD for Oncology, 3rd Edition morphology codes.For details on ascertainment of outcomes, please refer to **Chapter 3, Section 3.5**.

7.3.2.4 Statistical analysis

Women contributed person-years from the date of recruitment until the earliest of the date of invasive cancer registration (excluding non-melanoma skin cancer, ICD-10 code C44), date of death or loss to follow-up, or the last date of follow-up (31 December 2018). For analysis of risk of CIN3, follow-up was additionally censored at a woman's 65th birthday as she would no longer be eligible for routine screening on the NHS Cervical Screening Programme (NHSCSP). Cox proportional hazard regression models, with time in study as the underlying time variable, were used to calculate hazard ratios (referred to as relative risks [RR]) and corresponding 95% confidence intervals (CI) for CIN3/ICC associated with each OC exposure variable. Tests for trend were calculated as appropriate and took the duration of use within a particular category to be the median value within that category. For time since last use, tests for trend used the categorical variable coded by the midpoint of each category. Tests of heterogeneity in the relationship between invasive cervical cancer and OC use by histo-type were performed using a competing risks approach. [19] (see **Chapter 3 Section 3.6**)

All analyses were stratified by year of birth and year of recruitment and adjusted for region of recruitment, socioeconomic status, education, smoking status, body mass index (BMI), parity and age at first birth, use of MHT and for individual screening history. For details on coding of adjustment variables, please refer to **Chapter 3 Section 3.6.2**

Relative risks adjusted for socioeconomic status and region of recruitment only are referred to as RR1 and those additionally adjusted for education, smoking status, BMI, parity and age at first birth and MHT use are referred to as RR2. Finally, relative risks as in RR2 and additionally adjusted for screening history are referred to as RR3.

7.3.3 Results

7.3.3.1 Study participants

A total of 865,820 and 835,069 women were included in analyses for risk of ICC and risk of CIN3 respectively. The vast majority of women were past users of OCs (<0.002% current users at recruitment). Ever use of OCs was reported by 523 504 (60%) women, among whom the mean duration of use was 7.1 years with 94% having last use 10 or more years at last contact.

Table 7.5 summarises personal characteristics at recruitment in analyses of risk of ICC according to OC use. Compared to women who reported ever using OCs, never users were more likely to be older; to be from a lower socioeconomic background; to be less educated; to be obese; to have no screening test record (i.e., to have never attended for screening during the screening history period); and to be nulliparous. A higher proportion of women who were ever users were also current smokers and users of menopausal hormones than those who were never users.

Due to the additional exclusions for analyses of risk of CIN3 (**Section 7.3.2.4**), I had information on 835,069 women, with 60% reporting ever use of OCs. Baseline characteristics by OC use for these analyses were similar to those for analyses of risk of ICC and are presented in **Appendix Table E.1**.

7.3.3.2 Oral contraceptives and the risk of cervical neoplasia

Relative risks from models that only adjusted for region and socioeconomic status (RR1) were similar to multivariable-adjusted models (RR2) and both are presented in **Figures 7.1-7.3**. Further adjustment for screening (RR3), slightly strengthened

estimates for ICC and SCC (around 10% for SCC), but had little effect for CIN3 and no effect for AC. Only RR3 is reported in the following text.

Risk of ICC

A total of 1 016 cases of ICC were diagnosed during a median follow up time of 19.6 years. Among cases, 59% reported ever use of OCs, the mean duration of use was 7.6 years. Most women had stopped using OCs many years before recruitment (96% having last use 10+ years prior to recruitment).

There was no significant association with ICC for ever users, and no significant trend in risk for duration of use within ever users (trend:p=0.10) or time since last use within past users. (trend: p=0.24) (see **Figure 7.1**) Women who had used OCs more recently had also, on average, used them for a longer duration. For example, women who had last used OCs less than 25 years previously had a mean duration of use of 8.9 years, whereas women who had last used OCs 35 years or more previously had a mean duration of use of 5.4 years. For each year of use of OCs, a borderline significant increase in risk was seen in users upto 30 years since last use but there was no significant trend beyond 30 years after cessation (RRs [95% CI]: 1.02 [1.00-1.06] for 1.01 [0.98-1.04] <30 years and 30+ years since last use respectively) as shown in **Table 7.6**.

Risk of CIN3

A total of 1 465 cases of CIN3 were diagnosed during a median follow up time of 8.8 years, with 72% ever users of OCs. The mean duration of use in cases was 8.0 years with 91% having last used OCs 10+ years prior to recruitment.

Compared with never users, ever users of OCs had a 25% higher risk of CIN3 (**Figure 7.2**). The relative risk of CIN3 increased significantly with increasing duration of use (trend: $p<0 \cdot 001$), and was highest in ever users of 10+ years (RR: 1.49, 95% CI: 1.29-1.72 vs. never users), declining to that of never users after 25 years since last use (RR: 1.06, 95% CI: 0.90-1.25 for 25-30 years since last use vs. never users; trend: p<0.001). When duration of use was analysed within time since last use categories, there was no significant risk trend for CIN3 in either category of

time since last use (RRs [95% CI]: 1.00 [0.99-1.03] and 1.02 [0.99-1.05] for women <25 and 25+ years since last use respectively).

Histological subtypes

Of 1,016 cases of invasive cancer, 581 (57%) were SCC and 273 (27%) were AC. Ever use of OCs was reported by 64% and 54% of SCC and AC case women respectively. There was significant heterogeneity by histo-type in relation to all categories of OC use (heterogeneity: all p<0.001).

Compared with never users, ever users of OCs had a 33% higher risk of SCC (**Figure 7.3**). The relative risk of SCC increased significantly with increasing duration of use in ever users (trend: p<0.001), and was highest in users of 10+ years (RR: 1.62, 95% CI: 1.29-2.04), compared to never users. The risk of SCC also significantly declined with increasing time since last use (trend: p<0.001). For each year of use of OCs, a significant increase in risk of SCC remained upto 30 years after use had ceased, but there was no significant trend with increasing duration in women more than 30 years after cessation (RRs [95% CI] 1.02 [1.01-1.06] and 1.01 [0.97-1.05] for <30 and 30+ years since last use respectively).

Conversely, ever users of OCs had a 28% lower risk of AC (RR: 0.72, 95% CI: 0.56-0.94) compared to never users, although this risk did not significantly decrease with increasing duration in ever users (trend: p=0.47). There was also no significant trend seen with increasing time since last use for AC (trend: p=0.66). There were no significant associations for AC with duration regardless of time since last use.(**Table 7.7**)

7.3.4 Discussion

7.3.4.1 Overall findings

This prospective analysis has investigated the risks of cervical neoplasia associated with past use of OCs, adjusting for screening history. After almost 20 years of follow-up, the main findings in this study are as follows: 1) relative risks of CIN3 increased with increasing duration of OC use and declined after cessation of use;

2) there appeared to be little evidence of an effect of OC use on the risk of ICC; 3) there was substantial heterogeneity by histo-type for risk of cervical cancer associated with OC use, with some evidence of a reduction in risk of AC in users of OC; 4) the increased risk of SCC associated with increasing duration of OC use persisted for upto 30 years after cessation of use; and 5) adjustment for screening history strengthened relative risk estimates for SCC associated with OC use by about 10%, but had little effect on all other outcomes.

7.3.4.2 Comparison with previous evidence

The Collaboration reported an increased risk of CIN3/CIS in long-term users of OCs that diminished with increasing time since last use, which was also found in this analysis. By contrast, however, in this cohort the risk of ICC was not significantly associated with duration or recency of use of OCs– a finding which appears to be at odds with the results of the Collaboration who reported a significant risk trend for each timing variable, as well as independent effects with cross-classification.[6] However, this investigation was carried out in women who at recruitment had nearly all used OCs more than 10 years previously, which may explain the apparent lack of effect. This difference may also be partly explained by the significantly inverse associations found by histological subtype in users of OCs i.e. an increase in the risk of SCC but a reduction in the risk of AC associated with contraceptive use, which may have diluted risks for overall ICC.

As far as I am aware, the reduction in risk of AC in users of OCs is a novel finding and therefore also in contrast to the Collaboration meta-analysis on histo-types, where current use of OCs was associated with an increased risk per year of use of both SCC and AC, that declined with increasing time since last use. The disparity in results may at least partly be related to the inclusion of adenosquamous carcinomas (26% of AC cases) in the category of adenocarcinomas in the meta-analysis.[8] The squamous component of these cancers has recently been suggested to be stronger and/or appear earlier in carcinogenesis,[260] and may have therefore influenced the Collaboration results.The difference in results may also be partially related

to the effect of organised screening, which has changed the distribution of ICC worldwide.[54, 262] Since the start of organised screening, there has been a trend of decreasing incidence of SCC whose precursor lesions are detectable,[120] but a relative and absolute increase in the incidence of AC,[97] for which screening has been shown to be less effective.[98, 190] As many of the cases in the meta-analysis were diagnosed before the onset of screening or in areas of the world where screening is less available, it may be that the high number of adenosquamous carcinomas obscured true associations between adenocarcinomas and OCs as cervical screening is associated with reduced risk of adenosquamous carcinoma.[260] Nevertheless, the apparent reduction in risk of ACs in users of OCs this study was an interesting finding and the reason for this is unclear.

A key finding in this study is the persistent risk for invasive cervical cancers of squamous morphology with longer duration of use of OCs upto three decades after cessation of use. This risk persists for far longer than previously reported for squamous tumours and overall ICC by the Collaboration (10 years)[6, 8] and others (12 years).[255] Because this increase in risk persists upto 30 years after use has ceased, the public health implications of past OC use need further study in the context of older (long-term) users exiting screening programmes.

7.3.4.3 Possible mechanisms

The mechanisms by which OC use increases the risk of cervical neoplasms are not entirely clear. The use of OCs is suggested to promote persistence or progression of oncogenic HPV infections via constituent sex hormones (mainly oestrogen). Oestrogens are thought to enhance the expression of HPV 16 oncogenes and stimulate the degradation of tumour suppressor genes, enhancing the ability of the viral DNA to induce carcinogenesis.[263] Laboratory based studies in HPV-16 expressing transgenic mice have found that oestrogen and its nuclear receptor promote squamous cell carcinogenesis in combination with HPV oncogenes.[9] The findings in this chapter are compatible with this evidence and the increase in risk of invasive SCC associated with OC use may be attributed to these mechanisms.

Two biological mechanisms can be hypothesised to explain a difference in the risk of cervical cancer between sub-types in relation to OC use. First, is that cervical adenocarcinomas may represent a histological entity that resembles endometrial cancer. Combined OCs (which have higher concentrations of progesterones vs oestrogens) and progesterone-only contraceptives have been proposed to act via anti-oestrogenic mechanisms promoting atrophic and anti-proliferative effects on the endometrium. These effects are believed to underlie their protective effects against endometrial cancer and may be similar for cervical adenocarcinoma.[264] Studies in transgenic mice have also reported that progesterone inhibits cervical carcinogenesis[10] and more studies on different OC preparations especially progestin-based contraceptives in relation to AC are needed. Second, there is growing evidence to suggest that the small proportion of cervical cancers that are thought to be HPV-negative are morphologically adenocarcinomas.[265, 266] As mentioned, OCs are hypothesised to influence ICC risk via enhanced expression of HPV oncogenes. It is therefore possible that their effect on HPV-negative AC may be different and more evidence from other studies, especially those with information on HPV status, is needed to determine whether the inverse association reflects some residual confounding or points to a true biological mechanism.

7.3.4.4 Strengths and limitations

A major strength of these analyses is the prospective design, which helped minimise differential recall of exposure history amongst women with and without cervical cancer (a potential weakness of studies with retrospective assessment of exposure as discussed in **Section 7.2.4**). Second, this is one of the largest studies to date, allowing for a relatively more reliable comparison of histo-types than previous studies. The long-follow up in this study has also allowed for the assessment of risks associated with OC use in later life. Finally, the linkage of screening records with detailed information on timing and results of previous screens, has provided an unique opportunity to attempt to account for confounding by screening history as much as possible.

A weakness of these analyses is the lack of information on potential confounding factors: HPV status and sexual behaviour. However, previous studies have shown broadly similar results in studies adjusting for HPV or restricting to HPV positive women.[6, 11] Screening history results i.e., previous abnormalities were also included as adjustment in this study and are likely a proxy for persistent HPV infection which correlates directly with the development and severity of abnormalities.[231] Therefore, in this case, although these results may tell us little about the possible mechanisms by which OCs affect HPV carcinogenesis (see **Figure 2.2, Chapter 2**), they are likely a reliable measure of the effects of OC use. The lack of information of sexual behaviour also limits the analyses on the role of OC exposure and the risk of cervical neoplasia. However, as discussed in **Chapter 6 Section 6.3.4.4**, age at first birth (included as an adjustment variable in my analyses) has been suggested to be a good proxy of age at first sexual intercourse. The adjustment for sexual behaviour variables in analyses in relation to hormonal contraceptive use has also been previously shown to not materially alter overall results, although based on smaller numbers than the Collaboration analyses. [253]

7.4 Conclusions

The prospective analyses presented in this chapter provide new evidence that, adjusting for screening history, an increased risk of squamous cell carcinoma in users of oral contraceptives persists for up to 30 years after use ceases. These results also provide some evidence for a protective effect of OC use for adenocarcinoma of the cervix and further investigation is warranted. Future studies should elucidate the biological mechanisms underlying these results.

7.5 Tables

Search strategy	
(#1)	((((((cervical neoplasm, uterine[MeSH Terms]) OR (uterine cervical neoplasm[MeSH Terms])) OR (cervical intraepithelial neoplasia, grade iii[MeSH Terms])) OR (cancers, squamous cell[MeSH Terms])) OR (carcinoma, squamous cell[MeSH Terms])) OR (adenocarcinoma[MeSH Terms]))
(#2)	((((((combined oral contraceptives[MeSH Terms]) OR (agents, contraceptive[MeSH Terms])) OR (hormonal contraceptive agents[MeSH Terms])) OR (oral contraceptive agents, hormonal[MeSH Terms])) OR (birth control[MeSH Terms])) OR (the pill))
((#1) AND (#2))Filters: from 2007 - 2021	

Table 7.1: Search strategy

Publication	Adjustment for confounding			Total Cases/ Population	Duration of use	RR(95% CI)	Time since last use	RR(95% CI)	Time since last use within duration of use categories		
	Screening history	Sexual behaviour[a]	HPV						Duration of use	Time since last use	RR(95% CI)
Individual participant data meta-analysis											
The Collaboration 2007 Exposure: OC	Yes [b]	Yes	Yes[c]	11 170/46 679	Never < 5 years ... 10+ years ...	**1.00 (ref)** 0.96 (0.88-1.30) ... 1.56 (1.40-1.72) Trend p< 0.0001 ...	Never Current users ... 10-14 years ...	**1.00 (ref)** 1.65 (1.49-1.81) ... 1.05 (0.93-1.06) Trend p< 0.0001 ...	Never <5 years 5+ years 	 Current user ... 10+ years Current user ... 10+ years	**1.00 (ref)** 1.09 (0.89-1.29) ... 0.93(0.79-1.07) Trend p=0.1 1.90 (1.69-2.13) ... 0.94 (0.80-1.08) Trend p< 0.0001
Prospective studies											
Vessey *et al.*, 2013[255] Oxford FPA Oral Contraceptive Study Exposure: OC	No	No[d]	No	61/17 032	Non-user <48 months ... 97+ months ...	**1.00 (ref)** 2.3 (0.8-7.1) ... 4.8 (2.0-12.9) ...	Non-user <48 months ... 337+ months ...	**1.00 (ref)** 4.3 (1.8-11.8) ... 1.6(0.0-12.6) ...	Non-user 1-72 months 73+ months 	 <48 months ... 145 months <48 months ... 145+ months	**1.00 (ref)** 2.9 (0.9-9.6) ... 2.0 (0.5-7.2) 5.3 (2.2-15.0) ... 3.2 (1.0-10.2)
Roura *et al.*, 2016[11] EPIC Study Exposure: OC	No	No	No	261/308 036	Never ≤ 1year ... 15+ years	**1.00 (ref)** 1.5 (0.9-2.4) ... 1.8 (1.1-2.9) Trend p=0.2	Current ≤ 5years ... 15+ years	**1.00 (ref)** 1.1(0.4-2.8) ... 1.0(0.4-2.5) Trend p=0.7			
Iversen *et al.*, 2017[256] RCGP Oral Contraceptive Study Exposure: OC	No	No	No	192/46 022			Never Current/<5 years 35+ years	**1.00 (ref)** IRR 2.32(1.24-4.34) ... IRR 0.51(0.16-1.67)			
Iversen *et al.*, 2021[254] Exposure: All HC, with concentration of ≤ 35 μg	No	No	No	3643/1 853 542	Never ≤ 1 year current use 10+ years current use ...	**1.00 (ref)** 1.34 (1.12-1.59) 1.55 (1.34-1.80) Trend p< 0.001 ...	Never **1.00 (ref)** Current/<1year 10+ years ...	 1.30 (1.20-1.42) 0.79 (0.65-0.97) Trend p< 0.001 ...	Never < 1 5+ years 	 >1-5 ... 10+ >1-5 ... 10+ years	**1.00 (ref)** 1.07 (0.87-1.31) ... 1.06 (0.81-1.40) 1.55 (1.27-1.89) ... 1.29 (0.65-2.56)
Retrospective (case-control) studies											
Urban *et al.*, 2012[257] Exposure= oral and injectable contraceptives	No	Yes	No	2182/3674			Never <10 years 10+ years	**1.00 (ref)** OR 1.38 (1.08-1.77) OR 1.01 (0.84-1.22)	Never <5 years 5+ years	**1.00 (ref)** <10 years 10+ years <10 years 10+ years	 OR 1.43 (0.94-2.18) OR 1.03 (0.81-1.30) OR 1.37 (1.05-1.78) OR 1.00 (0.78-1.27)
Nojomi *et al.*, 2008[258] Exposure: OC	No	No[e]	No	300/619	Duration per year	OR 1.04 (0.98-1.1)	8+ years since last use < 8 years since last use	**1.00 (ref)** 1.4 (1.01-2.1)			

Table 7.2: Characteristics and results of studies included on the risk of invasive cervical cancer in relation to oral contraceptive use

Abbreviations: HPV, human papillomavirus; RR, relative risk; CI, confidence interval;IRR, incidence rate ratio; RCGP, Royal College of General Practitioners; FPA, Family Planning Association; EPIC, European Prospective Investigation into Cancer and Nutrition

[a] Adjustment for lifetime number of sexual partners or age at first sexual intercourse

[b] Adjusted for likelihood of screening based on self report or knowledge of availability of screening in each country

[c] Analyses restricted to studies with HPV DNA tested by polymerase chain reaction (PCR)

[d] Analyses adjusted for age at first marriage as a proxy for sexual behaviour

[e] Analyses adjusted for age at first marriage, age at first birth and multiple marriages as proxy for sexual behaviour

Publication	Adjustment for confounding			Total Cases/ Population	Duration of use	RR(95% CI)	Time since last use	RR(95% CI)	Time since last use within duration of use categories		
	Screening history	Sexual behaviour[a]	HPV						Duration of use	Time since last use	RR(95% CI)
Individual patient data meta-analysis											
The Collaboration 2007	Yes[b]	Yes	Yes	5403/40 912					Never		**1.00 (ref)**
Exposure: OC									<5 years	Current user	1.42 (1.18-1.66)
Outcome: CIN3/CIS										10+ years	1.23 (1.05-1.41)
											Trend p=0.1
									5+ years	Current user	2.23 (1.99-2.47)
										10+ years	1.35 (1.13-1.57)
											Trend p< 0.0001
Prospective studies											
Roura *et al.*, 2016[11]	No	No	No	804/308 036	Never	**1.00 (ref)**	Current	**1.00 (ref)**			
Exposure: OC					≤ 1year	1.0 (0.8-1.3)	≤ 5years	0.7(0.5-1.0)			
Outcome: CIN3/CIS					...	...	...	...			
					15+ years	1.6 (1.2-2.2)	15+ years	0.6(0.4-0.9)			
						Trend p=0.01		Trend p=0.2			
Retrospective (case-control) studies											
Xu *et al.*, 2018[253]	Yes[c]	Yes	No	886/4522			Never	**1.00 (ref)**	Never		**1.00 (ref)**
Exposure- any HC[d]							Current	OR 1.48 (1.02-2.15)	<10 years	Current	OR 1.13 (0.73-1.75)
Outcome- CIN2/3							...	...	...		...
							10+ years	OR 0.94 (0.62-1.43)	15+ years	Current	OR 1.82 (1.22-2.72)
											Trend= 0.04
									<10 years	Past	OR 0.99 (0.62-1.59)
									...		...
									15+ years	Past	OR 1.14 (0.78-1.66)
											Trend= 0.75

Table 7.3: Characteristics and results of studies included on the risk of cervical intraepithelial neoplasia, grade 3 (CIN3) in relation to oral contraceptive use

Abbreviations: RR, relative risk; CI, confidence interval; HC, hormonal contraceptive

[a] Adjustment for lifetime number of sexual partners or age at first sexual intercourse

[b] Adjusted for likelihood of screening based on self report or knowledge of availability of screening in each country

[c] Adjusted for number of Pap smears within 5 years of case diagnosis

[d] Hormonal contraceptives include: the combined pill, progestagen-only pill, injections, IUDs with hormones, implants and vaginal rings.

Publication	Screening	Adjustment		Cancer type	Total Cases/ Population	Time since last use	RR(95% CI)	Duration within time since last use categories	
	Screening history	Sexual behaviour[a]	HPV					Time since last use	RR(95% CI) per year of use
Individual patient data meta-analysis									
The Collaboration 2007[8]	Yes[b]	Yes	Yes	SCC	1581/6408			Current	1.08 (1.06-1.09)
Exposure: OC								...	...
								10+ years	0.98 (0.96-1.00)
									Trend p< 0.001
				AC	321/5148			Current	1.07 (1.04-1.11)
								...	...
								10+ years	1.02 (0.97-1.07)
									Trend p< 0.001
Prospective studies									
Iversen *et al.*, 2021[254]	No	No	No	SCC	2720/1 853 542	Never	**1.00 (ref)**		
All HC, with concentration of $\leq 35\mu$g						Current/<1 year	1.31 (1.19-1.44)		
						1+ years	1.03 (0.92-1.15)		
				AC	626/1 853 542	Never	**1.00 (ref)**		
						Current/<1 year	1.29 (1.05-1.60)		
						1+ years	0.98 (0.77-1.24)		

Table 7.4: Characteristics and results of studies included on the risk of squamous cell (SCC) and adenocarcinomas (AC) of the cervix in relation to oral contraceptive use

Abbreviations: RR, relative risk; CI, confidence interval; HC, hormonal contraceptive
[a] Adjustment for lifetime number of sexual partners or age at first sexual intercourse
[b] Adjusted for likelihood of screening based on self report or knowledge of availability of screening in each country

	% (n) of women*	
	Never users	**Ever users**
Mean age at recruitment (SD)	57.7 (4.3)	55.1 (4.1)
Most deprived tertile	34 (117 235)	32 (165 598)
No educational qualifications	50 (167 642)	38 (195 744)
Body mass index 30+kg/m^2	19 (60 859)	16 (78 191)
No screening test record	5 (16 355)	1 (7 480)
Current smokers	17 (57 296)	21 (107 980)
Ever menopausal hormone therapy use	35 (119 715)	49 (256 146)
Nulliparous	15 (51 859)	9 (46 366)
Mean number of FTPs, parous (SD)	2.1 (1.4)	2.2 (1.2)
Age at first birth <18 years, parous	2 (6 201)	3 (14 268)

Table 7.5: Recruitment characteristics of women included in analyses of risk of ICC analyses in relation to never versus ever use of oral contraceptives

* unless otherwise indicated

Estimates calculated in women with no missing values

A. Invasive cervical cancer			
Time since last use	**Cases**	**Mean duration of use, years**	**RR3 (95% CI) per year of use**
< 30 years	282	7.4	1.02 (1.00, 1.06)
30+ years	301	6.1	1.01 (0.98, 1.04)
B. Cervical intraepithelial neoplasia, grade 3 (CIN3)			
Time since last use	**Cases**	**Mean duration of use, years**	**RR3 (95% CI) per year of use**
<25 years	517	8.8	1.00 (0.99, 1.03)
25+ years	487	5.4	1.02 (0.99, 1.05)

Table 7.6: Relative risks (RR3)[1] and 95% confidence intervals (CI) for A. invasive cervical cancer and B. cervical intraepithelial neoplasia, grade3 (CIN3) per year of use of oral contraceptives, within categories of time since last use

[1] Relative risk adjusted for region of recruitment, deprivation tertiles, education, smoking status, body mass index, parity, age at first birth, menopausal hormone therapy use and screening history;

Time since last use	Mean duration of use, years	Cases	RR3 (95% CI) per year of use	Cases	RR3 (95% CI) per year of use
		Squamous cell carcinoma		Adenocarcinoma	
<30 years	7.4	181	1.02 (1.01, 1.06)	57	0.99 (0.95, 1.05)
30+ years	6.1	173	1.01 (0.97, 1.05)	94	0.98 (0.93, 1.04)

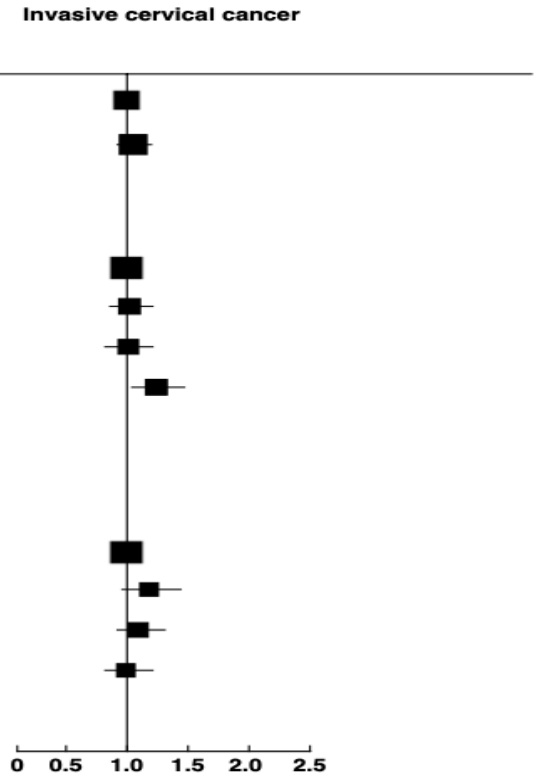
Table 7.7: Fully adjusted relative risks (RR3)[1] and 95% confidence intervals (CI) for invasive squamous cell and adenocarcinoma of the cervix per year of use of oral contraceptives, within categories of time since last use

[1] Relative risk adjusted for region of recruitment, deprivation tertiles, education, smoking status, body mass index, parity and age at first birth, menopausal hormone therapy use and screening history;

7.6 Figures

Figure 7.1: Relative risks (RR) and 95% confidence intervals (CI) of cervical cancer in relation to oral contraceptive use

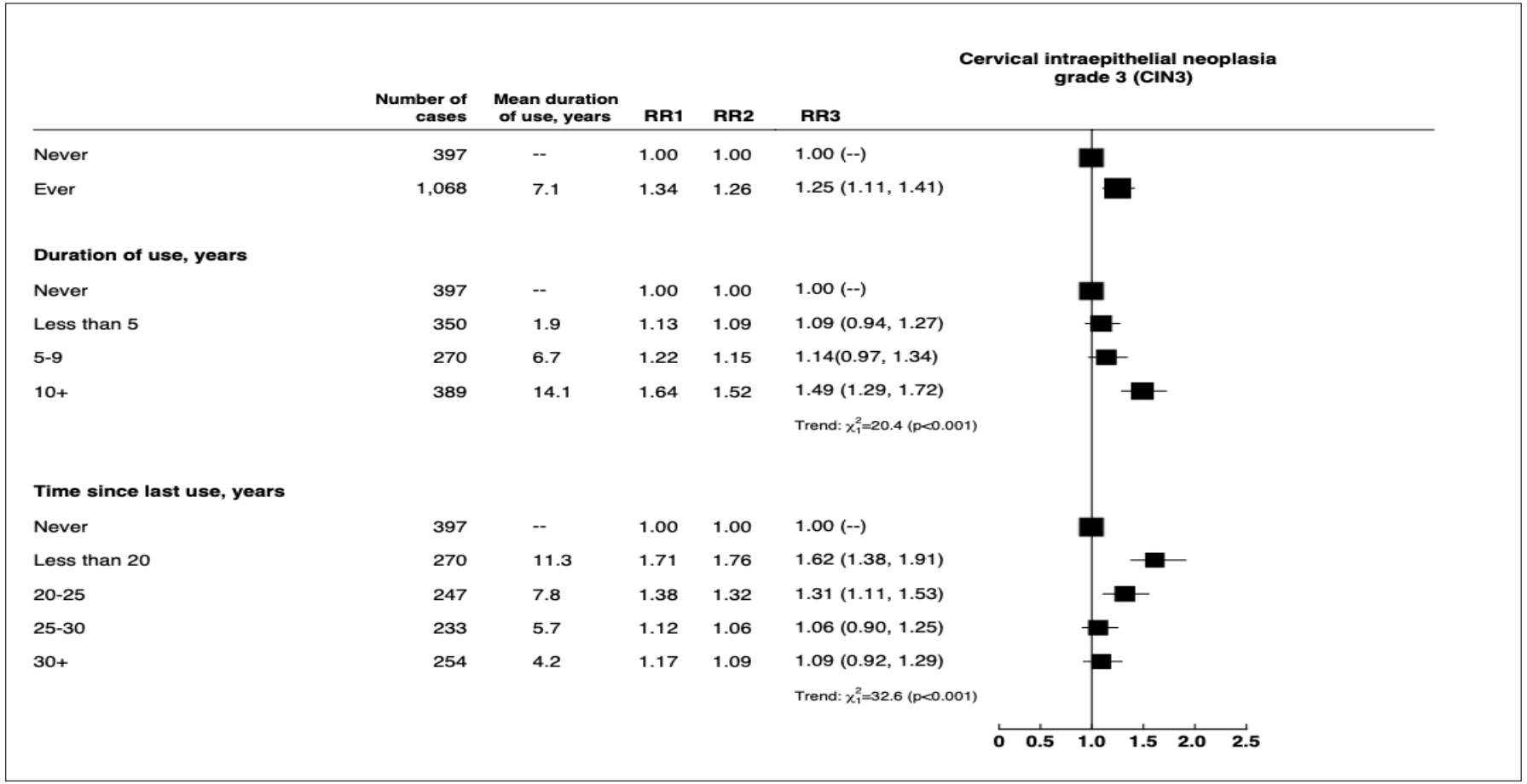
	Number of cases	Mean duration of use, years	RR1	RR2	RR3
Never	408	--	1.00	1.00	1.00 (--)
Ever	608	7.1	1.02	1.01	1.05 (0.92, 1.20)
Duration of use, years					
Never	408		1.00	1.00	1.00 (--)
Less than 5	224	1.9	0.96	0.97	1.02 (0.86, 1.21)
5-9	150	6.7	0.94	0.95	1.00 (0.82, 1.21)
10+	211	14.2	1.18	1.18	1.24 (1.04, 1.47)
					Trend: χ^2_1=2.7 (p=0.10)
Time since last use, years					
Never	408	--	1.00	1.00	1.00 (--)
Less than 25	165	8.9	1.11	1.11	1.18 (0.96, 1.44)
25-35	238	6.5	1.05	1.04	1.09 (0.92, 1.30)
35+	180	5.4	0.97	0.94	0.99 (0.82, 1.20)
					Trend: χ^2_1=1.4 (p=0.24)



RR1, relative risk adjusted only for region of recruitment and deprivation tertiles; **RR2**, relative risk adjusted for region of recruitment deprivation tertiles,education, smoking status, body mass index, parity age at first birth, menopausal hormone therapy; **RR3**, relative risk as in RR2 and additionally adjusted for screening history

Tests for trend calculated within ever users by duration and within past users by time since last use

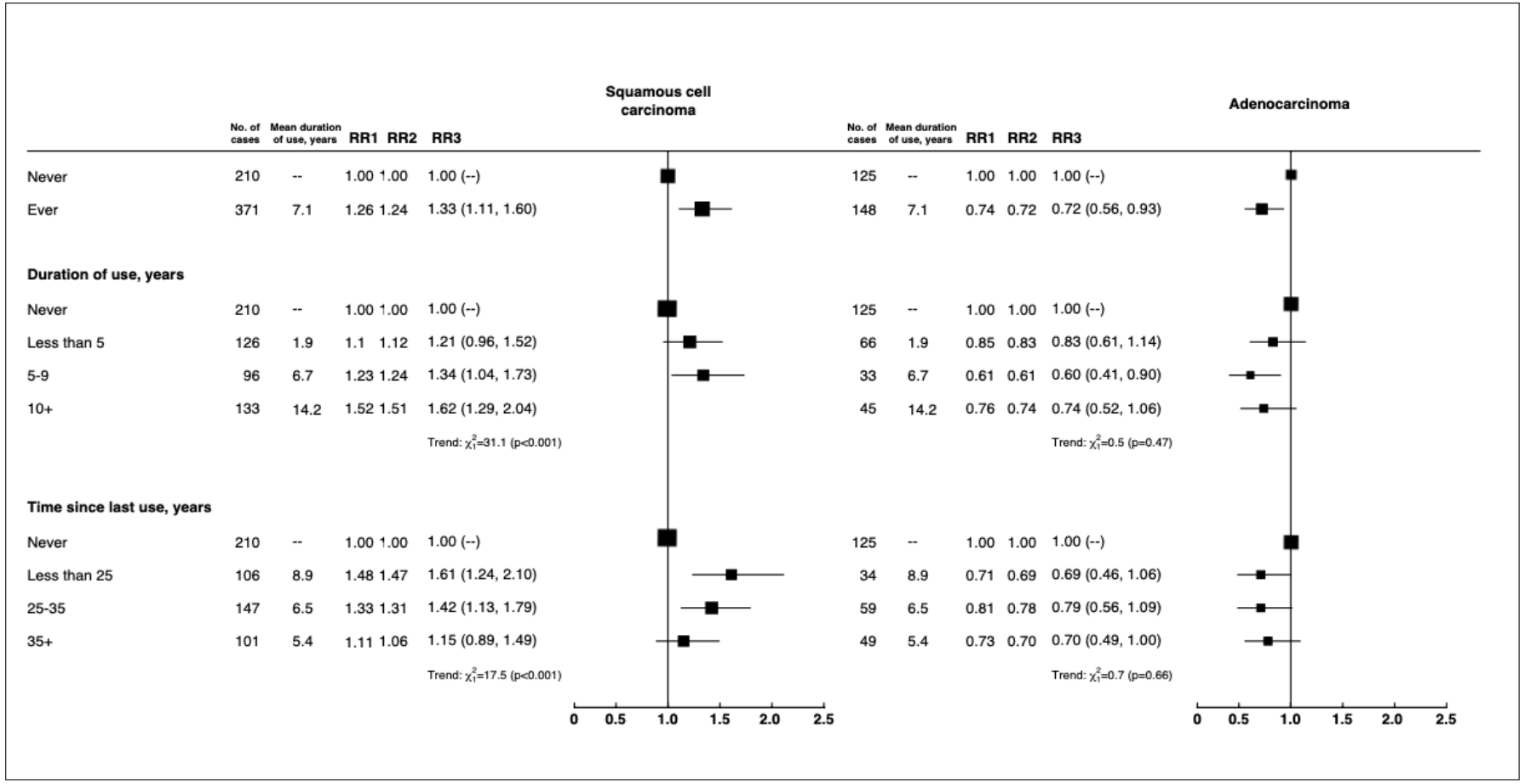
Figure 7.2: Relative risks (RR) and 95% confidence intervals (CI) of cervical intraepithelial neoplasia grade 3 (CIN3) in relation to oral contraceptive use



subcaption*__RR1__, relative risk adjusted only for region of recruitment and deprivation tertiles; **RR2**, relative risk adjusted for region of recruitment deprivation tertiles,education, smoking status, body mass index, parity, age at first birth, menopausal hormone therapy; **RR3**, relative risk as in RR2 and additionally adjusted for screening history

Tests for trend calculated within ever users by duration and within past users by time since last use

Figure 7.3: Minimally and fully adjusted relative risks (RR) and 95% confidence intervals (CI) of squamous cell and adenocarcinoma of the cervix in relation to oral contraceptive use



RR1, relative risk adjusted only for region of recruitment and deprivation tertiles; **RR2**, relative risk adjusted for region of recruitment deprivation tertiles,education, smoking status, body mass index, age at first birth, number of full-term pregnancies, menopausal hormone therapy; **RR3**, relative risk as in RR2 and additionally adjusted for screening history. **Tests for trend** calculated within ever users by duration and within past users by time since last use

We delight in the beauty of the butterfly but rarely admit the changes it has gone through to achieve that beauty

— Maya Angelou

8

Menopausal hormone therapy and the risk of cervical neoplasia

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8.1 Introduction

Previous chapters of this thesis have shown that sex-steroid hormones may be associated with cervical carcinogenesis. Women are exposed to endogenous hormonal changes induced by pregnancy (increased levels of oestrogen and progesterone), and **Chapter 6** of this thesis demonstrates that compared to nulliparity, parity is associated with an increase in the risk of invasive cervical cancer (ICC) and its immediate precursor, cervical intraepithelial neoplasia grade 3 (CIN3), which has been previously reported.[7] These associations were also reported in both major histological sub-types of ICC: squamous cell carcinoma (SCC) and adenocarcinoma (AC). Oral contraceptive (OC) use has also been previously found to be associated with cervical carcinogenesis.[6] **Chapter 7** has also shown evidence of significant heterogeneity in the effect of OCs by histo-type, with some evidence of a protective effect of OC use for AC, but persistently increased risks of SCC in OC users of longer durations.

Exogenous hormones in the form of menopausal hormone therapy (MHT) may therefore also be involved in the development of cervical tumours, but previous evidence on this relationship is extremely limited and inconsistent.[11–13, 267–270] In this chapter, I present the findings of a narrative review of previous evidence on MHT use and the incidence of cervical neoplasia i.e., CIN3 and overall ICC, including separately by major histo-type, SCC and AC. I then report on a detailed investigation of these relationships in the Million Women Study (MWS) cohort of postmenopausal UK women with prospectively collected information on MHT use and almost two decades of follow-up. Specifically, this study 1) evaluates the association between different measures of MHT use and risk of CIN3 and ICC overall; 2) examines the relationship between MHT use and ICC risk by tumour subtypes; and 3) investigates the effect of adjustment for screening history, as defined in **Chapter 5**, on risk estimates of cervical neoplasia in relation to MHT use.

8.2 Literature Review

8.2.1 Objectives

The aim of this review is to summarise previous evidence on the risk of cervical neoplasia i.e., CIN3 and ICC, including separately by major histo-type (SCC/AC) associated with use of MHT.

8.2.2 Methods

To summarise what is known on the risk of cervical neoplasia associated with MHT use, I conducted a literature search of online database PubMed for published evidence on MHT use in relation to cervical neoplasia to 1 August 2022. Search strategy is detailed in **Table 8.1**.

Any original studies (randomised controlled trial (RCT), systematic review, cohort or case-control) published in peer-reviewed journals examining the association between MHT use and the risk of cervical neoplasia were included. Studies were defined as "retrospective" if information on MHT use was recorded after CIN3/ICC diagnosis. Studies that reported any MHT use including systemic or vaginal use were included. Systemic MHT use was subdivided into oestrogen-only, oestrogen-progestagen, progestagen-only, tibolone, other, or unknown constituents.

The following study characteristics were extracted: study size; information on menopausal and hysterectomy status; MHT exposure including ever use, past/current use, duration of use, time since last use and constituent preparation of MHT; adjustment for screening history; and adjustment for other confounding. Maximally adjusted measures of risk of CIN3, ICC, SCC and AC associated with MHT use were extracted and are presented.

8.2.3 Results

The search identified 77 papers. I excluded 61 papers based on title and abstract review, leaving 16 articles which were examined in full text review, after which a total of seven studies were included on the association of MHT and cervical neoplasia.[11–13, 267–270] Study characteristics and results are briefly presented in text and in **Tables 8.2 and 8.4** for risk of ICC/CIN3 and SCC/AC respectively.

8.2.3.1 Risk of ICC

Six published studies have reported on the risk of ICC associated with MHT use (one RCT,[267] four prospective studies[11, 268–270] and one retrospective study[12]).

Anderson *et al.,* published a re-analysis of the Women's Health Initiative (WHI) RCT, a double-blind placebo-controlled trial including a total of 16,608 postmenopausal women who had not had a hysterectomy at baseline.[267] Women in the intervention arm of the trial (n=8,506) were treated with oestrogen-progestagen MHT and compared to women on a placebo pill (n=8502). After an average follow up of 5.6 years, a total of 13 cases of ICC were detected with no significant differences in risk found between intervention and control arms (HR: 1.44, 95% CI: 0.47-4.42 [8 exposed vs 5 unexposed cases]). While baseline characteristics were similar between groups, it is of note that during follow-up significantly more women had multiple Pap tests (71% vs 70%, $p<0.05$), and tests yielding low-grade abnormalities (8% vs. 6%, $p<0.001$) in the intervention versus placebo group. Although the definition of multiple testing is unclear, this finding suggests that women in the intervention group may have had more opportunities for the detection of cervical neoplasia.[267]

Of four prospective studies, Roura *et al.,* published an analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort reporting findings from 178,390 women aged 46-70.[11] Women who had not had a hysterectomy were included based on self-reported baseline menopausal status as perimenopausal (<9 menses in the past 12 months or age 46-55 years) or postmenopausal (no menses in the last 12 months, bilateral oophorectomy or age 55+ years). After a median of 9 years of follow-up with a total of 125 incident ICC cases for all users of

MHT (oestrogen-only, oestrogen-progestagen or progestagen-only), a statistically significant reduction in risk of ICC compared to never users [94 unexposed cases] was reported in ever users (RR: 0.5, 95% CI: 0.4-0.8 [31 exposed cases]) and current users (RR: 0.5, 95% CI: 0.3-0.8 [19 exposed cases]). There was no significant trend in risk of ICC with duration of MHT use (trend: p=0.4). (see **Table 8.2**) Results were also reported to be similar when restricted to postmenopausal women only, although data were not given. A borderline reduction in risk was also reported in ever versus never users of oestrogen-progestagen MHT, although no case numbers were given in these analyses (RR: 0.6, 95% CI: 0.3–1.0). It was reported that analyses on other MHT preparations such as oestrogen-only or progestagen-only were not possible due to small numbers. Findings on ever and current use were broadly similar in a nested case-control study adjusted for HPV serological markers (RRs vs. never users, [95% CI] 0.5, [0.4-0.8] with 18/72 cases vs. controls in ever users; and 0.5, [0.4-0.8] with 10/51 cases vs. controls in current users) and in analyses restricted to all cases and high-risk HPV sero-positive controls (RRs vs. never users, [95% CI] 0.3, [0.1-0.6] with 18/39 cases vs. controls in ever users; and 0.5, [0.4-0.8] with 10/29 cases vs. controls in current users).

Schneider *et al.,*[268] conducted a nested case-control analysis within the General Practice Research Database which primarily aimed to examine the risk of developing ICC associated with use of a specific oestrogen-progestagen MHT compound, known as estradiol/dydrogesterone (E/D), because the progestagen in this compound has been shown to be more pharmacologically similar to natural progesterone.[271] This analysis, therefore, compared postmenopausal women with a prescription record of E/D, and postmenopausal women with a record of other oestrogen-progestagen MHT to postmenopausal women who were non-users. From a total of 58 cases, they reported no statistically significant differences in the risk of ICC for E/D users (RR:0.25, 95% CI: 0.03–2.17 [1 exposed case]) or other oestrogen-progestagen MHT users (RR: 0.58, 95% CI 0.31–1.08 [21 exposed cases]) when compared to MHT non-users [36 unexposed cases]. (see **Table 8.2**) This study however did not provide

details on definition of menopause or hysterectomy status of women included, and it is possible that controls included women without a cervix.

Two older prospective studies similarly reported no statistically significant associations between the risk of ICC and MHT use.[269, 270] In the first, Persson *et al.,* reported on 22,597 women who had a mean age 54.5 years and a pharmacy record of receiving at least one prescription of oestrogen-only or oestrogen-progestagen MHT.[269] Overall, the number of observed cases of ICC in women receiving any MHT (n=38) was only slightly lower than that expected based on national incidence statistics (n=49.2), with a standardised incidence ratio (SIR) of 0.8, 95% CI: 0.6-1.1 when adjusted for hysterectomy and oophorectomy. Hunt *et al.,* included 4,544 British women aged 45-54 years recruited at specialist menopausal clinics around Britain from 1977-1982.[270] To be eligible, a woman had to be a current user of MHT who had received at least 1 year's continuous treatment with either oestrogen-only and oestrogen-progestagen MHT. Only 2 cases of ICC were observed at close of study compared to 4.25 expected on the basis of national incidence rates for women without a hysterectomy, with a corresponding SIR of 0.47, 95%CI: 0.05-1.70 reported. (see **Table8.2**)

Finally, Parazzini *et al.*,[12] compared 645 case women aged 40–75 years to 749 hospital controls of the same age who had not had a hysterectomy. Adjusting for menopausal status and lifetime number of cervical smears, when compared to never users [605/663 cases/controls], users of oestrogen-only MHT were reported to have a significant reduction in the odds of ICC (OR 0.5, 95% CI: 0.3-0.8 [40/86 exposed cases/controls]). The odds of ICC were also reported to significantly fall with increasing duration of ever use of oestrogen-only MHT (trend: $p<0.01$, although the trend estimate included never users and compared users of very short durations (OR: 0.6, 95% CI: 0.4-1.1 for <12 months use with 28/50 cases vs. controls and OR: 0.5, 95% CI: 0.2-1.0 for 12+ months use with 12/30 cases vs. controls, compared to never use). Compared to never users, women who had used oestrogen-only MHT within 10 years of index date were reported to have a relative risk of ICC of 0.9, 95%CI: 0.5-1.7 with 23/34 cases vs. controls, while

those who had taken them 10 or more years previously had a relative risk of ICC of 0.4, 95%CI: 0.2-0.7 with 17/46 cases vs. controls.

8.2.3.2 Risk of CIN3

To my knowledge, only two prospective studies have been published reporting on the risk of CIN3 associated with MHT use presented in **Table 8.3**.[11, 13] The first reported results from the above-mentioned analysis of the EPIC cohort by Roura *et al.,* including a total 280 cases of CIN3/CIS among 178,390 peri-menopausal and postmenopausal women.[11] For users of MHT, there was no significant association between ever use and risk of CIN3/CIS compared to never users (RR: 1.2, 95%CI: 0.9-1.5, [131 exposed vs 149 unexposed cases]), and for the same comparison, current use was associated with a borderline increase in risk (RR: 1.3, 95%CI: 1.0-1.7 [102 exposed cases]). There was no significant trend in risk of CIN3/CIS with duration of MHT use (trend: p=0.2). It was reported that similar results were obtained when analyses were restricted to postmenopausal women only, although data were not shown. The use of oestrogen-only MHT was reported to be associated with a non-significant increase in the risk of CIN3/CIS (RR: 1.7, 95%CI: 0.9-3.1, case numbers not reported), but a lack of association was reported for oestrogen-progestagen MHT, although data were not given. Finally, similar to main analyses, there were no significant associations with risk of CIN3/CIS in the nested case-control study adjusted for HPV serological markers or in analyses restricted to high-risk HPV seropositive women only.

Jaakkola *et al.,* reported on a cohort of 243,857 Finnish women who had not had a hysterectomy, were aged 50+ years (menopausal status not reported) and had used oestrogen-progestagen MHT for at least 6 months in 1994-2008. [13] After an average follow-up of 8.2 years, no significant associations were reported for ever use for the risk of both CIN3 and adenocarcinoma *in situ* (AIS) when compared with the expected rates in the general population (SIR 1.07, 95%CI: 0.92-1.23 [178/166.62 observed/expected cases] for CIN3 and SIR 1.38, 95%CI: 0.75–2.31

[14/10.17 observed/expected cases for AIS]). Longer duration of use of MHT (5+ years) was also not significantly associated with either CIN3 or AIS.

8.2.3.3 Histological subtypes

Two studies (one prospective,[13] one retrospective[272]) have published on the risk of ICC associated with MHT use by histo-type, although neither study reports a test for heterogeneity between the two. The above-mentioned Finnish prospective study by Jaakkola *et al.*, reported significant reduction in the risk of invasive SCC and a significant increase in the risk of invasive AC in ever users of oestrogen-progestagen MHT when compared with the expected rates in the general population (SIRs, [95%CI]: 0.41, [0.28–0.58] with 32/77.30 observed/expected cases for SCC and 1.31, [1.01-1.67] with 65/49.45 observed/expected cases for AC).[13] Although there were strong significant associations in users of longer duration (5+ years), they reported no significant heterogeneity between short-term (0.5-5 years) and long-term duration (5+) of use of MHT for the risk of both SCC (p=0.26) and AC (p=0.11). (see **Table 8.4**) Users of longer duration (10+ years) also had an increased risk of invasive AC (SIR: 2.72, 95%CI: 1.09-5.59) but there was no association with the risk of invasive SCC (SIR: 0.26, 95%CI: 0.01–1.46) and the trend was reported to be non-significant.

Lacey *et al.,* included a total of 124 cases of AC (33 *in situ* and 91 invasive) and 139 cases of SCC (48 *in situ* and 91 invasive), and compared them to 307 controls in women aged 18-65 years (84% pre-menopausal) without a hysterectomy who were using any MHT. Compared to never use, ever use of MHT was neither associated with the risk of SCC (OR: 0.85, 95%CI: 0.34-2.1, with 7/20 exposed cases vs. controls) nor the risk of AC (OR: 2.1, 95%CI: 0.95-4.6, with 13/20 exposed cases vs. controls). When stratified by MHT preparation, a significant increase in risk of AC was reported for use of oestrogen-only MHT (OR: 2.7, 95%CI: 1.1-6.8, 10/10 exposed cases vs. controls) but no association was reported for oestrogen-progestagen therapy (OR: 1.1, 95%CI: 0.26-5.0, 3/10 exposed cases vs. controls). Neither oestrogen-only (4/10 exposed cases vs. controls) nor oestrogen-progestagen MHT (3/10 exposed cases vs. controls) was reported to be significantly

associated with the risk of SCC as presented in **Table 8.4**. There were no significant associations for the risk of either histo-type for duration of use, time since last use or in analyses restricted to HPV-positive controls but numbers in these analyses were extremely small. Restriction to postmenopausal cases and controls was reported to have no effect on the oestrogen-only results for either SCC or AC, although data were not given and numbers would have been extremely limited.

8.2.4 Discussion

The evidence on the association between the use of menopausal hormones and the risk of cervical neoplasia is extremely limited. Broadly, there appears to be some suggestion of a reduction in the risk of ICC for ever users of MHT although this only reaches statistical significance in two of six reports.[11, 12] Results on timing of MHT use and the risk of ICC, including duration of use and time since last use are even more limited, and due to extremely small numbers little conclusion can be drawn from these analyses. Results on the risk of CIN3/CIS associated with MHT use also largely did not reach statistical significance, although there was some suggestion of a positive association between current use of MHT and the risk of CIN3/CIS.[11] When stratified by histology, there was some evidence of a reduction in risk of SCC and increase in risk of AC for ever users of MHT, although these associations were only statistically significant in one of two reports.[13] Although effects appeared to be stronger with increased duration of use of MHT for each histo-type, authors of this study[13] reported no evidence of heterogeneity between short and long-term use and no significant trend with increasing use in each histo-type. Neither study reported a test for heterogeneity between histo-types.[11, 13]

Reliable epidemiological assessment of the risk of ICC associated with MHT use requires large numbers and careful control of all potential sources of confounding and bias. In this regard, a number of shortcomings of previous evidence need to be considered. First, in several studies the number of cases included has been too small to reliably estimate any associations with resultant risk estimates having wide confidence intervals.[267–270] The potential role of chance in these findings

therefore cannot be excluded, for even studies with larger numbers of total cases had relatively few cases among users of MHT.[11, 12] Second, in assessing risks associated with the use of MHT to treat symptoms of the menopause, it is also important to consider potential confounding due to menopausal status. Menopause and time since menopause have been shown to be independently associated with the risk of breast cancer— another reproductive cancer influenced by endogenous and exogenous hormones.[273] Since the use of MHT is also strongly related to these characteristics, it has been demonstrated that there is substantial scope for confounding between the effects of the menopause and the effects of MHT on the risk of breast cancer; with failure to take menopause into account associated with an underestimation of the risk of breast cancer associated with the use of MHT.[273] The relationship between menopause, MHT and the risk of cervical cancer has received less attention. However, because like breast tissue, the transformation zone of the cervix (where most cervical cancers occur, see **Figure 2.1, Chapter 2**) is highly hormone-responsive,[274] there may well be potential for confounding by the menopause between the risk of ICC and MHT use due to changes in natural hormone concentrations around the menopause. Analyses of this relationship should therefore carefully classify a woman according to whether or not her ovaries are likely to be producing hormones cyclically and, the time elapsed since cyclical ovarian function was likely to have ceased—which is unclear in previous studies[11, 12, 268, 269]

Lack of information on hysterectomy status in previous studies is another potential source of bias, as women with hysterectomies may not be at risk for cervical cancer and as such risk estimates may be overestimated.[268–270]

Finally, only one study reported an adjustment for previous screening,[12] and there is potential for residual confounding by screening history in other reported findings. **Chapter 4** of this thesis has shown that women who are users of MHT may be more likely to attend for cervical screening. This may be because on collection of prescriptions users of MHT may be more likely to receive reminders to schedule appointments for cervical screening, or, in opportunistic screening settings they may have screening tests performed. As such, users of MHT may have different

opportunities for cervical neoplasia to be detected and treated and this difference could bias the results. For example, in the WHI trial where a non-significant increase in risk of ICC was reported, significantly more women had multiple Pap tests during follow-up in the intervention versus control arm,[267] and it is unclear what effect this difference could have had and/or whether it may have led to an earlier diagnosis of cervical cancer. Similarly, the reduced risk of ICC reported in other studies that did not include adjustment for previous screening[11] may potentially be overestimated because precursor lesions would have been detected and treated.

The association between the risk of cervical neoplasia and MHT use, with careful consideration of potential confounding by menopause and screening history, therefore needs to be clarified in prospective evidence with larger case numbers.

8.3 Menopausal hormone therapy and the risk of cervical neoplasia

8.3.1 Objectives

The analysis that follows will examine the risk of ICC, CIN3, SCC and AC in relation to MHT use, taking into account screening history as defined in previous chapters.

8.3.2 Methods

8.3.2.1 Study cohort

Data were obtained from the MWS with linked NHSCSP records. The methods of recruitment, data collection, follow-up, and ascertainment of cervical cancer for the MWS; and extraction and linkage with NHSCSP screening data have been described in detail in **Chapter 3**

A total of 9,782 women with missing information on MHT use were also excluded for both the risk of CIN3 and risk of ICC analyses of the 874,175 women eligible for inclusion for the analyses of the risk of ICC and 843,389 for the risk of CIN3 (see **Chapter 3, Section 3.6.1**). All analyses were restricted to postmenopausal women defined as those who reported at recruitment that their periods had stopped naturally or after bilateral oophorectomy or at age 55 years (since virtually all study participants (95%) who had not used MHT were postmenopausal at this age).[129] See **Section 8.3.2.4**

8.3.2.2 Exposure variable

The questions used to assess menopausal hormone use in this cohort have been described in **Chapter 3**. All analyses were restricted to MHT exposures defined based on the recruitment questionnaire only. This is because the response rates for resurveys, in median year 2001 (on average 3.3 years after recruitment) and 2006 (on average 7.5 years after recruitment), were 65% and 50% respectively and it would not be possible to update MHT use for all women.[129] Updating MHT use over time is explored in a sensitivity analysis described in **Section 8.3.2.4**

The first exposure examined was ever vs. never use at recruitment, which is expected to have very little misclassification. This is because although some post-menopausal never users or past users may have started MHT use after recruitment this is likely to have been relatively uncommon. In a subset of the MWS it has been shown by linking to GP records that before 2003, an estimated 1% of never users became current users and 4% of past users became current users annually.[252] These figures were much lower after 2003 at 0.1% and 0.2% respectively, because many women in the UK ceased MHT use after publication of the first results from the WHI trial in 2002 which reported that the use of MHT was associated with an increased risk of breast cancer, heart disease, stroke, and venous thromboembolism.[275] Further in the dataset used for my research, the proportion of women who were never and past users at recruitment who became current users at 3-year; and 8-year resurveys was only 4% and 2%; and 1.1% and 1.3% respectively.

The second exposures examined were "past use" and "current use" at recruitment, relative to never use. These analyses were done as a proxy of recency of use, as generally, women who reported current use at recruitment will have used MHT more recently than those who reported past use.

Analyses then examined the timing variables, duration of use and time since last use, relative to never users. As it is difficult to determine when women who reported current use of MHT at recruitment stopped use of MHT, timing variables were only examined in past users and categories in these analyses were: duration of use in past users (<3, 3+years) and time since last use in past users which was treated as a time-dependent variable and assumed to increment by 1 year for each year of follow-up after the date of last contact i.e. recruitment (<15,15+ years for ICC; and <10,10+ years for CIN3). Unlike **Chapter 7**, duration of use and time since last use of MHT were not strongly inter-related and mean duration of use was largely similar across all categories of time since last use. For example, women who had last used MHTs less than 5 years previously had a mean duration of use of 3.1 years, whereas women who had last used MHT 15 years or more previously had a mean duration of use of 2.5 years. Cross-classification of these variables was therefore not assessed.

Analyses stratified by constituent MHT preparations were not possible due to the exclusion of hysterectomised women in this study (see **Chapter 3, Section 3.6.1**). Oestrogen-only preparations are not usually given to women with a uterus because of the increased risk of endometrial cancer.[276–278] The MHT preparation prescribed is therefore largely determined by hysterectomy status and of a total of 322,183 women in these analysis with information on MHT type, the proportion using oestrogen-progestagen MHT was 85% and only 5% for oestrogen-only MHT at recruitment. However, given the hypothesis that oestrogen and progesterone may influence risk (see **Chapter 7, Section 7.3.4.3**), analyses were restricted to oestrogen-progestagen users in past and current users to explore effects of excluding other MHT with lesser oestrogenic/progestogenic activity such as tibolone.

8.3.2.3 Outcomes

The main outcomes of interest were cervical intraepithelial neoplasia, grade 3 [CIN3] International Classification of Diseases 10th Edition [ICD-10] code D06) and invasive cervical cancer [ICC](ICD-10 code C53). For analyses of histotype, the outcome was split into the two most common histological groups: squamous cell carcinoma and adenocarcinoma by combining ICD-10 codes with ICD for Oncology, 3rd Edition morphology codes. For details on ascertainment of outcomes, please refer to **Chapter 3, Section 3.5**.

8.3.2.4 Statistical analysis

Person-time for each woman was calculated from date of recruitment if they reported having a natural menopause or bilateral oophorectomy at recruitment, or were aged 55 or older; otherwise person-time was calculated from date of 55th birthday, until the earliest of the date of invasive cancer registration (excluding non-melanoma skin cancer, ICD-10 code C44), date of death or loss to follow-up or the last date of follow-up (31 December 2018). For analysis of risk of CIN3, follow-up was additionally censored at a woman's 65th birthday as she would no longer be eligible for routine screening on the NHSCSP. Cox proportional hazard regression models, with time in study as the underlying time variable, were used to calculate hazard

ratios (referred to as relative risks [RR]) and corresponding 95% confidence intervals (CI) for CIN3/ICC in relation to the different measures of MHT use. Tests of heterogeneity in the relationship between cervical cancer and MHT use by histotype i.e. SCC and AC were performed using a competing risks approach.[19] **(see Chapter 3 Section 3.6)** Due to small numbers of cases, the timing variables were not examined in analysis by histotype.

All analyses were stratified by year of birth and year of recruitment and adjusted for region of recruitment, socioeconomic status (SES), education, smoking status, body mass index (BMI), parity and age at first birth, use of oral contraceptives and for individual screening history. For details on coding of adjustment variables, please refer to **Chapter 3 Section 3.6.2**. Relative risks adjusted for SES and region of recruitment only are referred to as RR1 and those additionally adjusted for education, smoking status, BMI, parity and age at first birth and oral contraceptive use are referred to as RR2. Finally, relative risks as in RR2 and additionally adjusted for screening history are referred to as RR3.

Three sensitivity analyses were performed. The first aimed to assess the possibility of misclassification of MHT status in women who were entered into analyses as postmenopausal at 55th birthday but had reported their MHT status prior to menopause at recruitment i.e., women who may have reported never use of MHT but may have started use after recruitment. Analyses were therefore restricted to women reporting natural menopause or bilateral oophorectomy only and compared to main analyses to examine the effect of including these women. In the second, to keep confounding by factors associated with the menopause to a minimum, analyses restricted to postmenopausal women at recruitment were additionally adjusted for a defined time since menopause at recruitment (<5, 5-9, 10+ years). As discussed in **Section 8.2.4**, this is because the timing of menopause has been shown to be independently associated with the risk of breast cancer.[273] Given the hypothesis that ICC may also be a hormone-responsive cancer it is possible that there may be a risk of confounding between the effects of the menopause, and the effects of MHT, on the risk of cervical cancer.

The final sensitivity analysis explored the effect of updating MHT use over time. Information on MHT use reported at recruitment (in median year 1998) was, where possible, updated using information provided through resurveys in median year 2001 (on average 3.3 years after recruitment), and 2006 (on average 7.5 years after recruitment), to take account of changing patterns of MHT use beyond the date of the last completed questionnaire for example, current users becoming past users on later questionnaires. To avoid misclassification, MHT use was set to unknown 4 years after each survey unless a woman last reported use as never/past on the 2001 resurvey or on the 2006 resurvey. It was assumed that these women would not start/restart use because women were, on average, age 60 on the 2001 resurvey and 64 on the 2006 resurvey and few women start MHT after age 60.[252] This variable has been derived by investigators of the MWS but has not yet been used in publication. For more details on the rules used in defining this variable, please refer to **Appendix Table F.1** Due to insufficient case numbers, sensitivity analyses updating MHT use over time were not possible by histo-type.

8.3.3 Results

8.3.3.1 Study participants

Table 8.5 shows the recruitment characteristics of eligible participants (n=864,393), by use of MHT reported at recruitment in analyses for the risk of ICC. Ever users at recruitment differed primarily from never users of MHT in that they were more likely to have had a screening test record and to have ever used oral contraceptives, but less likely to be obese. Due to additional exclusions, I had information on 833,607 women for CIN3 analyses, with broadly similar characteristics as presented in **Appendix F, Table F.2**.

8.3.3.2 Menopausal hormone therapy and the risk of cervical neoplasia

Relative risks for the risk of ICC, including separately for SCC and AC, from models that only adjusted for region and socioeconomic status (RR1) were similar to models further adjusted for behavioural, reproductive and hormonal factors (RR2). For estimates of the risk CIN3, adjustment for personal factors attenuated risk estimates by about 10% with smoking status having the largest effect on estimates. Both RR1 and RR2 are presented in **Figures 8.1-8.3**. Further adjustment for screening (RR3) slightly attenuated estimates for ICC and SCC (approx. 10% for SCC), but had little effect for CIN3 and no effect for AC. Only RR3 is reported in the following text. Analyses examining current use were done as a proxy of recency of use, and current use at recruitment was taken as most recent use of MHT.

Risk of ICC

A total of 947 cases of ICC were diagnosed during a median follow up time of 18.9 years. Ever use of MHTs at recruitment was reported by 372 cases (39%) and the mean duration of use at recruitment was 2.6 years in past users.

Compared to never users, ever use of MHT was associated with a borderline reduction in risk of ICC (RR: 0.86, 95%CI: 0.75-0.99). Women who reported current use of MHT at recruitment also had a reduced risk of ICC compared to never users (RR: 0.81, 95%CI: 0.69-0.95), but there was no risk association with ICC for

those who reported past use at recruitment (RR: 0.94, 95%CI: 0.78-1.12). (**Figure 8.1**) For users of oestrogen-progestagen therapy (O+P), current use at recruitment was associated with a reduction in risk of ICC compared to never users (RR: 0.78, 95%CI: 0.65-0.93, [167 cases O+P MHT]), but there were no associations with past use (RR: 0.90, 95%CI: 0.71-1.15 [78 cases O+P MHT]). There were no significant associations with past use with increasing duration of use of all MHT (heterogeneity: p=0.55) or with increasing time since last use of all MHT (heterogeneity: p=0.40).

Risk of CIN3

A total of 1,255 cases of CIN3 were diagnosed during a median follow up time of 8.7 years. Ever use of MHT at recruitment was reported by about half of the cases, with a mean duration of MHT use of 2.1 years in past users.

The risk of CIN3 was not significantly associated with ever, past or current use of MHT at recruitment compared to never use (RRs vs. never use [95%CI] 1.02 [0.91-1.15], 0.94 [0.80-1.10] and 1.07 [0.94-1.22] respectively). There were also no associations with past or current use at recruitment relative to never use in users of oestrogen-progestagen MHT (RR: 0.86, 95%CI: 0.70-1.07 and RR: 1.13, 95%CI: 0.99-1.29 respectively)

There was some evidence of differences in risk in timing of MHT use in past users i.e., between shorter vs. longer duration of use (heterogeneity: p=0.04), although individual associations were not statistically significant. There were no significant association with time since last use (heterogeneity: p=0.07) (**Figure 8.2**)

Histological subtypes

Of the total 947 cases of ICC, 538 (57%) were SCC and 258 (27%) were AC. Of these 63% and 55% reported ever use of MHT respectively.

Tests for heterogeneity showed significant differences between histo-types according to ever use of MHT (heterogeneity: p<0.001). Compared to never users, ever use of MHT was associated with a small reduction in the risk of SCC, but was not associated with the risk of AC (RR: 0.80, 95%CI: 0.67-0.96 and RR: 1.07, 95%CI: 0.83-1.38 respectively). There was no evidence of heterogeneity in the

association between SCC and AC with current use at recruitment for all MHT (heterogeneity: p=0.2) or in analyses restricted to oestrogen-progestagen therapy in current users at recruitment (heterogeneity: p=0.07).

8.3.3.3 Sensitivity analyses

Sensitivity analyses left the main findings largely unchanged. In analyses to assess the effect of restricting analyses further to include only women who reported a natural menopause or bilateral oophorectomy at recruitment, the relative risk of ICC based on 110 and 97 incident cases was 0.98, 95%CI: 0.79-1.21 and 0.79, 95%CI: 0.63-0.99 for past and current users at recruitment respectively. This is similar to findings from the main analyses as presented in **Table 8.6**. Additional adjustment for time since menopause at recruitment in these restricted analyses altered the relative risks only at the second decimal place. Neither were there any material differences for CIN3 or SCC as presented in **Tables 8.6 and 8.7**. Relative risks associated with AC appeared to be somewhat stronger with adjustment for time since menopause, although numbers in these analyses are small with wide CIs.

Time-varying MHT

Due to the large reduction in case numbers for women who reported current use at recruitment, the confidence intervals for estimates in analyses updating use are wide as presented in **Table 8.6**. Relative risks estimates were broadly similar to main analyses, although point estimates appeared to be slightly attenuated for the risk of ICC but slightly stronger for the risk of CIN3.

8.3.4 Discussion

8.3.4.1 Overall findings

This prospective analysis has investigated the risks of cervical neoplasia associated with MHT use, adjusting for screening history, in a cohort of postmenopausal non-hysterectomised women. The main findings in this study are as follows: 1) ever use of MHT may be associated with a small reduction in the relative risk of ICC compared to never use, but there is no evidence of associations with past use for increasing duration or time since last use; 2) use of MHT reported as current at study recruitment, which was taken as the most recent use of MHT, was also associated with a reduction in the risk of ICC; 3) neither ever use nor current use at recruitment were significantly different from never use in relation to the risk of CIN3, although there was some suggestion of different risks of CIN3 in relation to duration of use of MHT in past users but the numbers in these analyses are too small to answer this question definitively; 4) there was significant heterogeneity in the associations with ever MHT use between histo-types, with a small reduction in relative risk for SCC but no significant associations with AC; and 5) the risk of cervical neoplasia associated with MHT use was slightly attenuated by previous screening history.

8.3.4.2 Comparison with previous evidence

Few previous data show any significant associations between the use of MHT and the risk of ICC—a finding which is somewhat at odds with my results. Randomised trial evidence from the WHI trial were reported to be too limited to suggest there is any association between incidence and ever MHT use.[267] Similarly, when compared to never users, ever use and current/recent use of MHT only appeared to be associated with a significant reduction in risk of ICC in only two[11, 12] of a total of five observational studies.[11, 12, 268–270] However, the overall lack of statistically significant associations may be explained by the small numbers of observed cervical cancers meaning studies were likely under-powered and risk estimates yielded were imprecise with wide CIs.

A non-significant increase in the risk of CIN3 associated with ever use relative to never use of MHT has been previously reported,[11, 13] and was also found in this study. Little association between the risk of CIN3 and current use of MHT has also been previously reported.[11] There were no associations with duration of use in previous studies and findings from my analyses that suggest some differences in risk of CIN3 in relation to duration of use require further investigation with larger numbers.

The reduction in risk of ICC seen with ever use varied significantly between the two histological types. Although results of two previous studies have been suggestive of variation, neither reported a formal test for heterogeneity.[13, 272] As in my analyses, ever use of MHT has been previously associated with a significant reduction in the risk of SCC.[13, 272] However, in contrast to the lack of association with the risk of AC observed in my analyses, a significant increase in risk that appeared to strengthen with increasing duration of use has been reported previously.[13] It may therefore be that the lack of association with AC in my analyses may be related to differences in duration of use, but data are too sparse to make meaningful comparisons.

Most women in these analyses were users of combined oestrogen-progestagen therapy, and effects of MHT use appeared to be similar in analyses comparing current users of oestrogen-progestagen MHT only at recruitment to never users which provides some support to the hypothesis that any effects may be exerted via sex-steroid hormones. Although some previous studies have reported effects stratified by MHT type,[11, 272] case numbers in these analyses, where reported, have been very small ($n < 10$) and any differences cannot be distinguished from chance.

To my knowledge, this is the first study to report on the effect of adjustment for screening history on risk estimates associated with MHT use. A single previous study has reported including an adjustment for lifetime number of cervical smears, but the effect of this adjustment was not reported.[12]

8.3.4.3 Strengths and weaknesses

A major strength of this study is that this cohort has a much larger number of incident cases of ICC in ever users of MHT compared to previous studies allowing for more reliable analyses. For example, in analyses for the risk of ICC, this study had 372 exposed cases of ICC compared to 40 in the previous largest study[12]. The relatively large number of cases also enabled this study to more reliably explore heterogeneity by histo-type (201 SCC and 115 AC exposed cases in these analyses vs. 32 SCC and 65 AC overall cases in previously largest study[13]). Another strength of this study compared to previous evidence is the detailed individual information collected as part of the MWS, allowing for more careful consideration of relevant confounding in these analyses. For example, owing to detailed information on menopausal status this study was able to restrict all analyses to postmenopausal women i.e., those who would have received MHT for treatment of menopausal symptoms, minimising confounding by the menopause as much as possible. These analyses have also been able to exclude women who had had a hysterectomy who may not be at risk of cervical neoplasias; the inclusion of hysterectomised women as part of study populations has been previously estimated to result in lower incidence of cervical cancer in the postmenopausal age categories.[279, 280] Finally, as discussed in previous chapters, this study benefits from having linked routinely collected NHS cervical screening records for study participants which were included as adjustment minimising potential confounding by selective screening.

These analyses are subject to some limitations. First, the main limitation is the limited ability to analyse associations with MHT use updated over time due to attrition. The main analyses therefore assumed that never users would not start and past users would not restart during follow-up, although sensitivity analyses showed this assumption to be reasonable. Similarly, these analyses were unable to look at duration of use in current users as a result of limited information on MHT use over time. Second, although this study had more cases of each histo-type than any previous study, analyses exploring the associations between MHT use and risk of ICC by histo-type were also under-powered, particularly for analyses on the

risk of AC. Finally, although many known risk factors for ICC such as OC use and smoking were examined as potential confounders here, other risk factors such as sexual behaviour variables were not recorded in this study and could not be taken into account in these analysis. As discussed in previous chapters (see **Chapters 6 and 7)**, to mitigate potential confounding, these analyses have adjusted for age at first birth, which has been shown to be a good proxy for age at first sexual intercourse.[246] It is also of note that the risk of ICC associated with sexual behaviour is primarily due to the acquisition of new HPV infections.[74] Therefore, older women who would be using MHT are likely to have been already exposed to HPV with any infections likely to be persistent,[232] and confounding by sexual behaviour can expected to be minimal. The lack of information on HPV status is also a shortcoming of this study. However, again as discussed in previous chapters, it is expected that the use of the screening history variable including previous abnormalities minimises any potential confounding by HPV status. Furthermore, broadly similar results for risk of cervical neoplasia associated with MHT use have been found in analyses adjusted for HPV status as well as restricted to HPV positive women,[11] suggesting it is possible to reasonably rule out a large confounding effect due to HPV infection in the association.

8.3.4.4 Possible mechanisms

Possible mechanisms responsible for the apparent MHT-associated prevention of ICC are unclear. Menopausal hormone therapies generally have higher concentrations of oestrogens vs. progesterones and therefore the reduction in risk seen for ICC and for SCC, appears to be in contrast to previously proposed mechanisms relating to oestrogen-induced carcinogenesis discussed in **Chapters 6 and 7**. It may be possible that hormonal constituents have different effects over a woman's reproductive life-course as has been hypothesised as an explanation for differences seen between effects of exogenous hormones i.e., use OCs vs. MHT, in other hormonally-responsive cancers such as ovarian cancer.[281] There is also evidence that although oestrogens have been shown to modulate tumour initiation e.g. in breast tissue, they can

suppress tumour development e.g. in the colon.[282] A biological mechanism proposed for this protective effect, if causal, is the differential expression of oestrogen receptors: ERα and ERβ, and the theory that binding of oestrogens to ERα induces a cancer-promoting response, whereas ERβ binding is protective.[283] Both oestrogen receptors are expressed in cervical tissue,[284, 285] and there is some experimental evidence suggesting a protective role of ERβ in cervical cancer.[286] However, there is little consensus on this hypothesis overall and further research specifically in relation to cervical cancer is needed. Results showing some suggestion of a different risk of adenocarcinoma with MHT use also warrant further biological research to elucidate potential mechanisms.

8.3.5 Conclusions

In a large cohort of UK women with prospectively collected information on exposures, and almost 20 years of follow up, I found some evidence to suggest that ever use and more recent use of menopausal hormone therapy may be associated with a reduction in the risk of incident invasive cervical cancer, and the effect of MHT appears to be strongest for tumours with squamous cell morphology.

8.4 Tables

Search strategy	
(#1)	(cervical intraepithelial neoplasia, grade iii[MeSH Terms]) OR ((((cancer of cervix[MeSH Terms]) OR (cancer of the uterine cervix[MeSH Terms])) OR (cancers, uterine cervical[MeSH Terms])) OR (disease, uterine cervical[MeSH Terms]))
(#2)	((((((hormone replacement therapies[MeSH Terms]) OR (hormone replacement therapy[MeSH Terms])) OR (hormone replacement therapy, post menopausal[MeSH Terms])) OR (postmenopausal hormone replacement therapy[MeSH Terms])) OR (therapies, hormone replacement[MeSH Terms])))
	((#1) AND (#2))

Table 8.1: Search strategy

Study design	Publication	Study participants	Exposure	Adjustment for confounding		Total Cases/ Population	Ever use (95% CI) [cases]	Past/current use (95% CI) [cases]	Duration of use	(95% CI) [cases]	Time since last use	(95% CI) [cases]
				Screening	Other							
Invasive cervical cancer												
RCT	Andersonet *al.*, 2003[267]	Postmenopausal women without a hysterectomy	Intervention O+P MHT daily vs. placebo	N/A	N/A	13/16 608	Never 1.00 (ref) [5 unexposed cases] HR 1.44 (0.47-4.42) [8 exposed cases]	—	—	—		
Prospective	Roura *et al.*, 2016[11]	Peri-menopausal[a]and postmenopausal women without a hysterectomy	Self-reported MHT use (O-only, P-only or O+P)	No	BMI, marital status, education, physical activity, smoking, number of FTPs, OC use	125/178 390	Never 1.00 (ref) [94 non-exposed] RR 0.5 (0.4-0.8) [31 exposed]	Never 1.00 (ref) [94 non-exposed] RR for past 0.6 (0.3-1.2) [11 exposed]) RR for current 0.5 (0.3-0.8) [19 exposed]	Never <1 year ... 5+years	1.00 (ref) [94 non-exposed] RR 0.7 (0.4-1.2 [12 exposed] ... RR 0.4 (0.2-0.9) [7 exposed] Trend in ever users:p=0.4	—	—
	Schneider *et al.*, 2009[268]	Women mean age 51.3 years (SD 6.1), menopause or hysterectomy status not reported	Prescription record of either E/D (O+P) or other O+P	No	BMI, smoking, OC use, MHT use before index date	58/406	Never 1.00 (ref) [36 unexposed] OR for E/D 0.25 (0.03-2.17) [1 exposed]; OR for other O+P 0.58 (0.31-1.08) [21 exposed]	—	—	—	—	—
	Persson *et al.*, 1996[269]	Women mean age 54.5 years, menopausal status not reported.	Pharmacy record of O-only or O+P MHT	No	Oophorectomy and hysterectomy	38/22 597	SIR 0.8 (0.6-1.1) [38 observed vs. 49.2 expected]					
	Hunt *et al.*, 1987[270]	Postmenopausal women	Current users of O-only or O+P MHT	No	No	2/4544	—	SIR for current 0.47 (0.05-1.70) [2 observed vs. 4.25 expected[b]]	—	—	—	—
Retrospective	Parazzini *et al.*, 1997[12]	Non-hysterectomised women aged 40-75, menopausal status definition not reported	Self-reported O-only or O+P MHT	Yes[c]	Menopausal status, number of sexual partners, age, social class, parity, OC, smoking	645/1394	Never 1.00 (ref) [605/663 unexposed cases/controls] OR 0.5 (0.3-0.8) [40/86 exposed cases/controls]	— —	Never <12 months 12+ months	1.00 (ref) OR 0.6 (0.4-1.1) [28/50 exposed cases/controls] OR 0.5 (0.2-1.0) [12/30 exposed cases/controls] Trend including never users: p<0.01	Never < 10 years 10+ years	1.00 (ref) OR 0.9 (0.5-1.7) [23/34 exposed cases/controls] OR 0.4 (0.2-0.7) [17/46 exposed cases/controls]

Table 8.2: Characteristics and results of studies included on risk of invasive cervical cancer in relation to use of menopausal hormone therapy (MHT)

Abbreviations: RCT, randomised controlled trial; BMI, body mass index; FTPs, full term pregnancies; OC, oral contraceptives; CI, confidence interval; HR, hazard ratio; RR, relative risk; OR, odds ratio; SIR, standardised incidence ratio; AIS, adenocarcinoma *in situ*; CIS, carcinoma *in situ*; O-only, oestrogen-only MHT; P-only, progestagen-only MHT; O+P, oestrogen-progestagen MHT

[a] Peri-menopausal defined as <9 menses in the past 12 months or age 46-55 years

[b] Expected rate based on national incidence rates in women without a hysterectomy

[c] Adjusted for lifetime number of cervical smears.

Study design	Publication	Study participants	Exposure	Adjustment for confounding		Total Cases/ Population	Ever vs. never use (95% CI) [cases]	Past/current vs. never use (95% CI) [cases]	Duration of use	(95% CI) [cases]	Time since last use	(95% CI) [cases]
				Screening	Other							
Cervical intraepithelial neoplasia, grade 3 (CIN3)												
Prospective	Roura *et al.*, 2016[11] **Outcome**: CIN3/CIS	Peri-menopausal[a]and postmenopausal women without a hysterectomy	Self-reported MHT use (O-only, P-only or O+P)	No	BMI, marital status, education, physical activity, smoking, number of FTPs, OC use	280/178 390	Never 1.00 (ref) [149 unexposed]	Never 1.00 (ref)	Never	1.00 (ref)	—	—
							RR 1.2 (0.9-1.5) [131 exposed]	RR for past 1.0 (0.6-1.5) [22 exposed]) RR for current 1.3 (1.0-1.7) [102 exposed]	<1 year ... 5+years	RR 1.3 (0.9-1.9) [43 exposed] ... RR 1.0 (0.7-1.6) [27 exposed] Trend in ever users:p=0.2		
	Jaakkola *et al.*, 2011[13] **Outcome**: CIN3 or AIS	Non-hysterectomised women, aged 50+ years, menopausal status not reported	Record of use of O+P MHT	No	No	192/243,954	SIR for CIN3, 1.07 (0.92-1.23) [178 observed vs. 166.62 expected] SIR for AIS, 1.38 (0.75-2.35) [14 observed vs. 10.17 expected]	—	—	—	—	—

Table 8.3: Characteristics and results of studies included on risk of cervical intraepithelial neoplasia grade 3 (CIN3) in relation to use of menopausal hormone therapy (MHT)

Abbreviations: RCT, randomised controlled trial; BMI, body mass index; FTPs, full term pregnancies; OC, oral contraceptives; CI, confidence interval; HR, hazard ratio; RR, relative risk; OR, odds ratio; SIR, standardised incidence ratio; AIS, adenocarcinoma *in situ*; CIS, carcinoma *in situ*; O-only, oestrogen-only MHT; P-only, progestagen-only MHT; O+P, oestrogen-progestagen MHT; NR, not reported

[a] Peri-menopausal defined as <9 menses in the past 12 months or age 46-55 years

[b] Expected rate based on national incidence rates in women without a hysterectomy

[c] Adjusted for lifetime number of cervical smears.

Study design	Publication	Participants	Exposure	Adjustment for confounding		Cancer type	Total Cases/ Population	Ever vs. never use (95% CI) [exposed cases/controls]*	Past/current vs. never use (95% CI) [exposed cases/controls]*	Duration of use	(95% CI) [exposed cases/controls]*	Time since last use	(95% CI) [exposed cases/controls]*
				Screening	Other								
Prospective	Jakkaola *et al.*, 2011[13]	Non-hysterectomised women, aged 50+ years, menopausal status not reported	Record of use of O+P MHT	No	No	SCC	32/243 857.	SIR 0.41 (0.28-0.58) [32 observed vs. 77.30 expected]	—	0.5-5 years	SIR 0.66 (0.38-1.08) [16 observed vs. 24.09 expected]	—	—-
										5+ years	SIR 0.34 (0.16-0.65) [9 observed vs. 26.21 expected]		
											Heterogeneity: p= 0.26[a]		
										10+ years	SIR 0.26 (0.01-1.46 [NR]		
						AC	65/243 857	SIR 1.31 (1.01-1.67) [65 observed vs. 49.45 expected]	—	0.5- 5 years	SIR 0.73 (0.38-1.27) [12 observed vs. 16.49 expected]	—	—-
										5+ years	SIR 1.83 (1.24-2.59) [31 observed vs. 16.97 expected]		
											Heterogeneity: p= 0.11[a]		
										10+ years	SIR 2.72 (1.09-5.59 [NR]		
Retrospective	Lacey *et al.*, 2000[272]	Women aged 18-65 years (84% pre-menopausal) without a hysterectomy.	Self-reported use of any MHT (O-only, O+P)	No	Age, race	SCC	139/446	Never 1.00 (ref) [287/132]	—	Never	1.00 (ref) [287/132]	Never	1.00 (ref) [287/132]
								OR 0.85 (0.34–2.1) for any MHT [7/20]	—	<3 months	2.0 (0.53-7.7) [4/5]	<2 years	0.19 (0.02-1.5)
								OR 0.86 (0.26-2.8) [4/10] for O-only	—	...	...	2+ years	1.9 (0.62-5.9) [6/7]
								OR 0.85 (0.21-3.4)[3/10] for O+P	—	>12 months	0.25 (0.03-2.0) [1/10]		
						AC	124/446	Never 1.00 (ref) [287/109]	—	Never	1.00 (ref) [287/109]	Never	1.00 (ref) [287/109]
								OR 2.1 (0.95–4.6)for any MHT [13/429]	—	< 3 months	3.5 (1.0-12.2) [6/5]	< 2 years	1.2 (0.34-3.9) [4/13]
								OR 2.7 (1.1-6.8) [10/10] for O-only	—	...	...	2+ years	3.4 (1.2-9.5) [9/7]
								OR 1.1 (0.26-2.8) [3/10] for O+P	—	>12 months	1.7 (0.52-5.6) [5/10]		

Table 8.4: Characteristics and results of studies included on risk of squamous cell and adenocarcinoma in relation to use of menopausal hormone therapy (MHT)

Abbreviations: SCC, squamous cell carcinoma; AC, adenocarcinoma; OR, odds ratio; CI, confidence interval; NR, not reported
SIR, standardised incidence ratio; O-only, oestrogen-only MHT; O+P, oestrogen-progestagen MHT
* unless otherwise indicated
[a] Heterogeneity test between duration of use 0.5-5 years and 5+ years

Characteristics at recruitment	% (n) of women* Never users	Ever users
Mean age at recruitment (SD)	56.3 (4.7)	55.9 (4.1)
Most deprived tertile	33 (161 794)	31 (120 709)
No educational qualifications	44 (211 656)	41 (151 341)
Body mass index 30kg/m^2 and over	19 (85 201)	15 (53 654)
No screening test record	4 (19 699)	1 (4194)
Current smokers	18 (85 569)	21 (79 504)
Ever oral contraceptive use	54 (211 656)	68 (151 341)
Nulliparous	12 (58 263)	11 (40 089)
Age at first birth <18 years, parous	2.5 (10 140)	3.1 (10 283)

Table 8.5: Characteristics of women at recruitment in relation to never versus ever use of menopausal hormone therapy

* unless otherwise indicated

Estimates calculated in women with no missing values

	Invasive cervical cancer			Cervical intraepithelial neoplasia, grade 3 (CIN3)		
	Number of cases never-use/past/current use	Relative risk (95%CI) versus never use of MHT*		Number of cases never-use/past/current use	Relative risk (95%CI) versus never use of MHT*	
		Past	Current		Past	Current
Main analyses	**575/162/210**	**0.94 (0.78-1.12)**	**0.81 (0.69-0.95)**	**644/203/408**	**0.94 (0.80-1.10)**	**1.07 (0.94-1.22)**
Including only women with natural menopause or bilateral oophorectomy at recruitment adjusted as in main analyses	464/110/97	0.98 (0.79-1.21)	0.79 (0.63-0.99)	470/134/183	0.96 (0.79-1.16)	1.07 (0.90-1.28)
As above with additional adjustment for time since menopause	464/110/97	0.96 (0.78-1.19)	0.77 (0.61-0.97)	470/134/183	0.94 (0.77-1.14)	1.04 (0.87-1.24)
Time-varying MHT	351/181/84	0.96 (0.79-1.17)	0.89 (0.66-1.20)	471/198/266	0.79 (0.67-0.93)	1.15 (0.99-1.35)

Table 8.6: Sensitivity analyses - effects of restriction to postmenopausal women only at recruitment; of additional adjustment for time since menopause; and of varying use of MHT over time on relative risks of invasive cervical cancer (ICC) and cervical intraepithelial neoplasia, grade 3 (CIN3)

* Relative risk adjusted for region of recruitment and deprivation tertiles, education, smoking status, body mass index, parity and age at first birth and oral contraceptive use and screening history

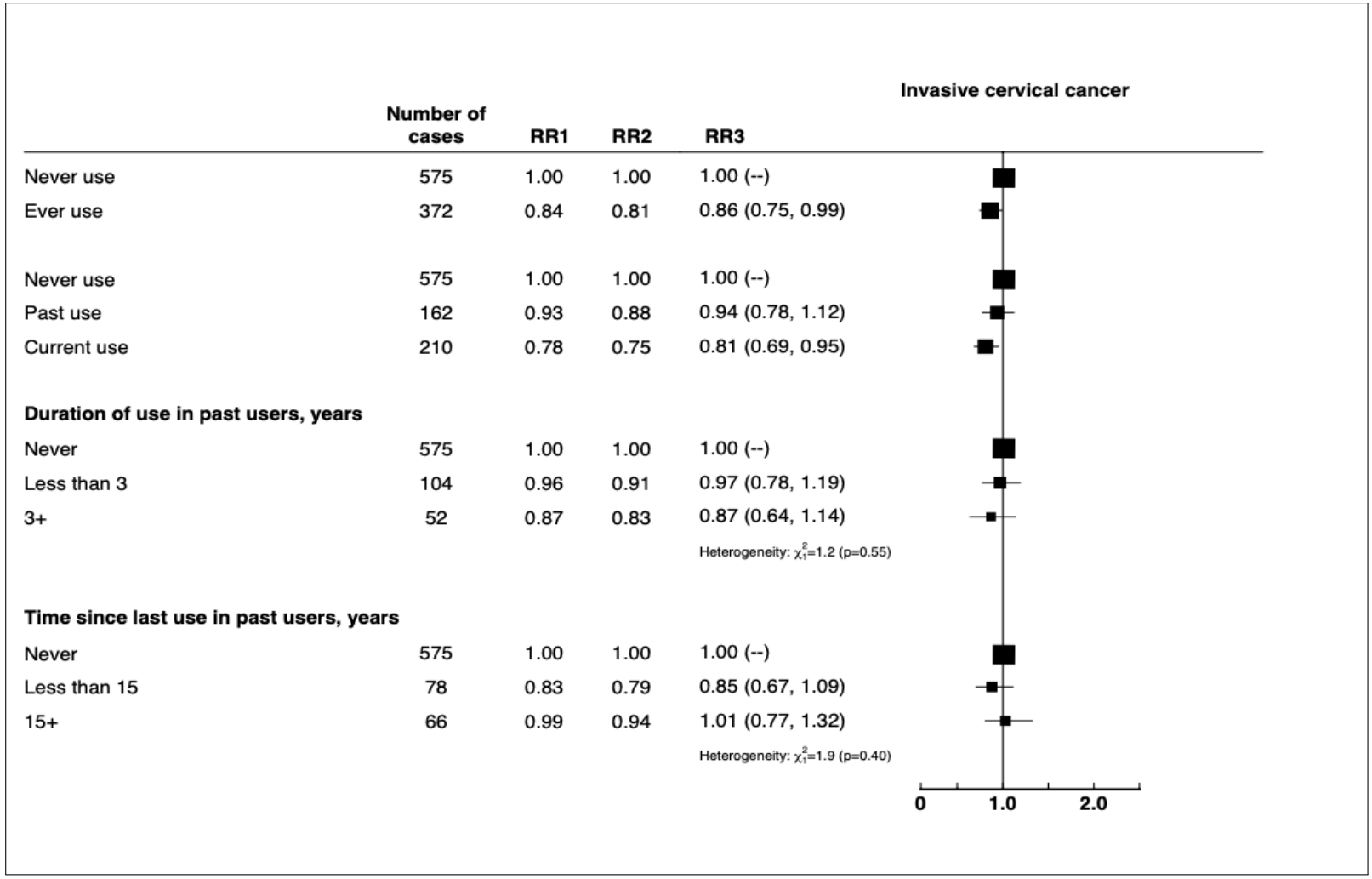
	Squamous cell carcinoma		Adenocarcinoma	
	Number of cases never-use/ever	Relative risk (95%CI) of ever versus never use of MHT*	Number of cases never-use/ever	Relative risk (95%CI) of ever versus never use of MHT*
Main analyses	**337/201**	**0.80 (0.67-0.96)**	**143/115**	**1.07 (0.83-1.38)**
Including only women with natural menopause or bilateral oophorectomy adjusted as in main analyses	286/112	0.78 (0.62-0.98)	103/64	1.24 (0.90-1.71)
As above but with additional adjustment for time since menopause	286/112	0.75 (0.60-0.95)	103/64	1.24 (0.89-1.72)

Table 8.7: Sensitivity analyses - effects of restriction to postmenopausal women only at recruitment and of additional adjustment for time since menopause on relative risks of invasive squamous cell and adenocarcinoma of the cervix

* Relative risk adjusted for region of recruitment and deprivation tertiles, education, smoking status, body mass index, parity and age at first birth and oral contraceptive use and screening history

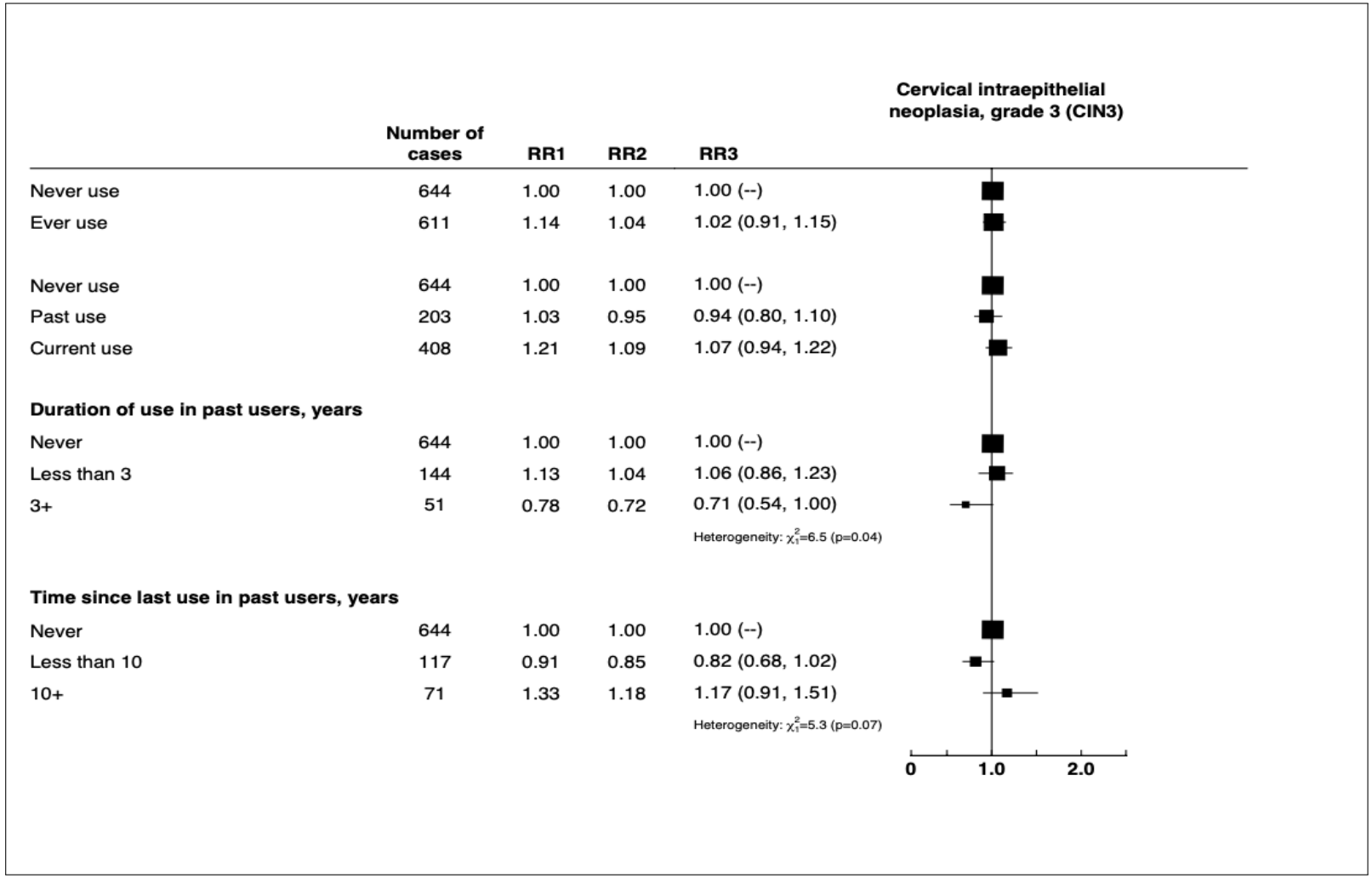
8.5 Figures

Figure 8.1: Relative risks (RR) and 95% confidence intervals (CI) of invasive cervical cancer in relation to menopausal hormone therapy use reported at recruitment



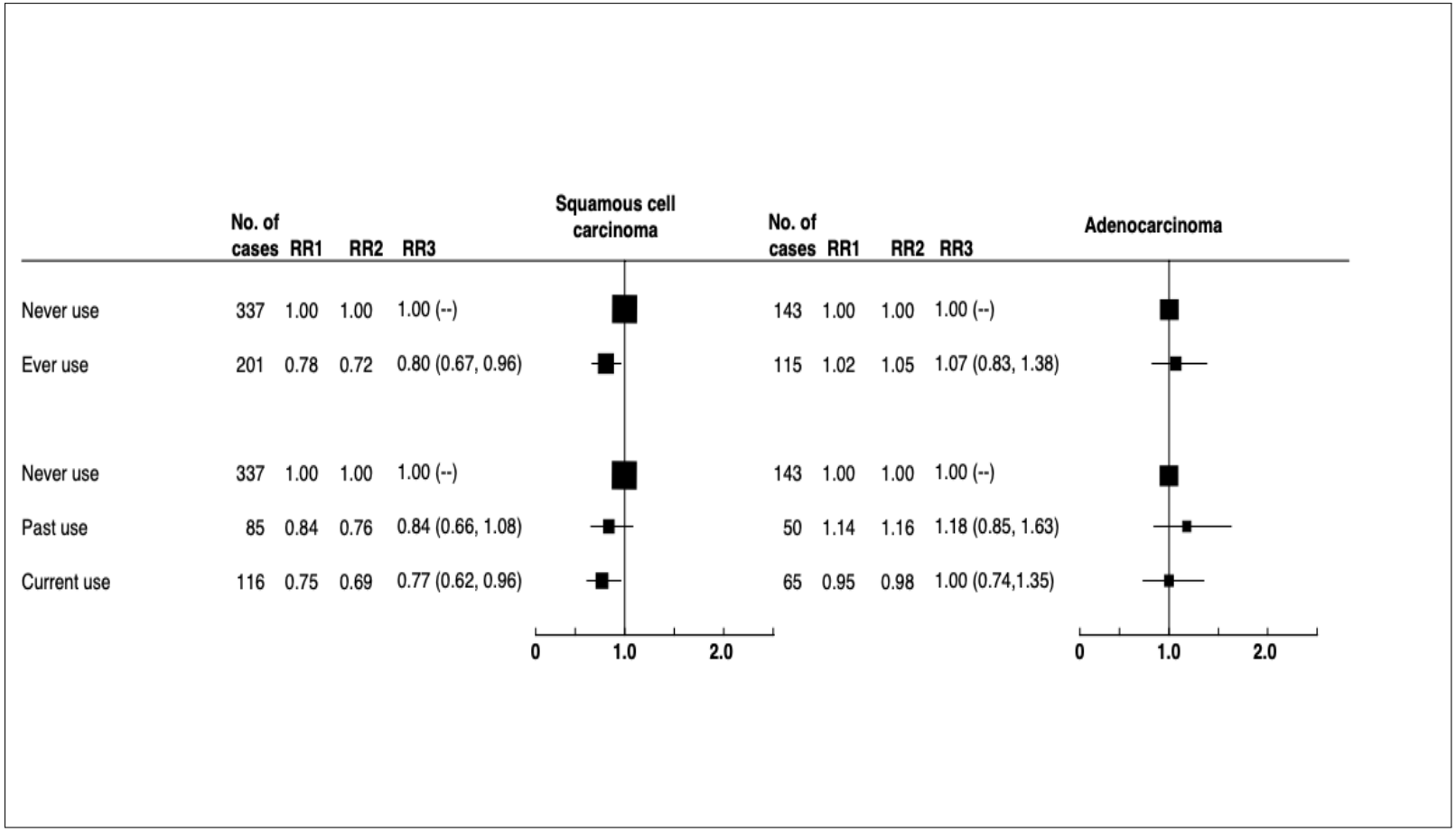
RR1, relative risk adjusted only for region of recruitment and deprivation tertiles; **RR2**, relative risk adjusted for region of recruitment deprivation tertiles,education, smoking status, body mass index, parity and age at first birth, oral contraceptive use; **RR3**, relative risk as in RR2 and additionally adjusted for screening history

Figure 8.2: Relative risks (RR) and 95% confidence intervals (CI) of cervical intraepithelial neoplasia grade 3 (CIN3) in relation to menopausal hormone therapy use reported at recruitment



RR1, relative risk adjusted only for region of recruitment and deprivation tertiles; **RR2**, relative risk adjusted for region of recruitment deprivation tertiles,education, smoking status, body mass index, parity and age at first birth, oral contraceptive use; **RR3**, relative risk as in RR2 and additionally adjusted for screening history

Figure 8.3: Minimally and fully adjusted relative risks (RR) and 95% confidence intervals (CI) of squamous cell and adenocarcinoma of the cervix in relation to menopausal hormone therapy use reported at recruitment



RR1, relative risk adjusted only for region of recruitment and deprivation tertiles; **RR2**, relative risk adjusted for region of recruitment deprivation tertiles,education, smoking status, body mass index, parity and age at first birth, oral contraceptive use; **RR3**, relative risk as in RR2 and additionally adjusted for screening history

"We have not yet arrived, but every point at which we stop requires a re-definition of our destination"

— Ben Okri

9 Discussion and conclusions

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9.1 Introduction

The overall aim of this thesis was to investigate the effect of the adjustment for screening history on the association between reproductive and hormonal factors and the risk of cervical neoplasia i.e. high-grade precursor lesions (cervical intraepithelial neoplasia, grade 3 [CIN3]) and invasive cervical cancer (ICC) including separately by major histological tumour type, squamous cell carcinoma (SCC) and adenocarcinoma (AC). Specifically, this thesis: 1) examined the association between personal factors, including reproductive and hormonal factors, and cervical screening non-attendance; 2) examined the association between previous screening history and the risk of cervical neoplasia; 3) evaluated the associations between parity including number of full-term pregnancies (FTP) and age at first FTP and the risk of cervical neoplasia adjusting for screening history; and 4) examined the associations between oral contraceptive (OC) and menopausal hormone therapy (MHT) use and the risk of cervical neoplasia adjusting for screening history. This chapter summarises key findings, their potential mechanisms, public health implications and finally recommendations for future research.

9.2 Main findings

The main findings of this thesis, as described in **Chapters 4 to 8** are summarised below

9.2.1 Factors influencing non-attendance for organised cervical screening programmes in England

The analyses in **Chapter 4** confirmed that English women who do and do not attend for cervical screening are considerably different not only by age and socioeconomic status, as has been reported previously,[142–148] but also by behavioural, reproductive and hormonal factors. The largest effect was seen for parity, where nulliparous women were seven-times more likely to be non-attenders compared to parous women. Non-attendance was also associated with obesity, current smoking,

giving birth at younger ages, multiparity and never use of OCs or MHT. The analyses also showed that all these personal factors were significantly associated with poor versus good attendance. This finding is of interest because it provides further evidence on the strong association between attendance for screening and personal factors including reproductive and hormonal factors i.e. personal factors influence not only non-attendance vs. attendance but differences according to these factors exist within attenders as well.

9.2.2 The definition of the screening history variable

The findings from **Chapter 5** support previous evidence that previous screening attendance is strongly associated with the risk of cervical neoplasia.[16] Specifically, that women who do not attend for screening are more likely to develop ICC. These analyses also showed a persistently elevated risk of cervical neoplasia for women who had previous abnormalities detected at screening, and particularly high-grade abnormalities. There was also evidence of significant heterogeneity in the associations with screening history by histological tumour type with strong positive associations between screening history, in terms of both previous attendance and previous abnormalities, and the risk of SCC but little to no association between screening history and the risk of AC.

These analyses in conjunction with those in the previous chapter confirm the strong associations of screening history, defined as both previous attendance and abnormality, with both exposures and outcome in this thesis. There is therefore substantial potential for confounding by screening history–justifying adjustment for this variable, as defined, in subsequent analysis chapters.

9.2.3 Reproductive factors, screening and the risk of cervical neoplasia

The analyses in **Chapter 6** confirmed with the largest number of prospective cases to date that childbearing is associated with an overall increase in risk of ICC. However, there was no significant increase in risk of ICC with increasing

number of FTPs among parous women after adjustment for age at first FTP. These analyses also showed that age at first FTP was independently associated with the risk of ICC, with a strongly increased risk of ICC with decreasing age at first FTP which remained significant even after adjustment for number of FTPs. There was no evidence of significant heterogeneity in the risk of ICC associated with either number of FTPs or age at first FTP by histo-type. The pattern of associations with the risk of CIN3 was similar to that of ICC, although a significant trend with increasing number of FTPs remained even after mutual adjustment.

These analyses have also for the first time shown evidence of a large effect of adjustment for screening history on associations between parous vs. nulliparous women. In my analysis, when comparing parous vs. nulliparous women, adjustment for screening history strengthened estimates for the risk of ICC and largest effect of adjustment was seen for tumours of squamous morphology, where risk estimates were increased by about 50%. There were, however, no effects of adjustment for screening in analyses restricted to parous women only. Previous studies, which have been largely limited in their assessment of screening history, have reported no material effect of adjustment for screening history on estimates for the risk of cervical neoplasia associated with reproductive factors.[7] It is worth noting, however, that the findings in my research may be driven by the large differences in attendance between nulliparous and parous women in shown in **Chapter 4 (see Table 4.5**), which may reflect specific/unknown differences in this cohort.

9.2.4 Oral contraceptives, screening and the risk of cervical neoplasia

Chapter 7 of this thesis has shown that the risk of CIN3 associated with OC use was increased with increasing duration of use, but waned with increasing time since last use. These findings are largely similar to previous evidence.[6] However, this thesis has contributed novel information on the association between OC use and risk of ICC by tumour histotype showing significant heterogeneity between histotypes, with inverse associations observed in ever users of OC for the risk of

AC in contrast to positive associations for the risk of SCC. Consequently, although the risks of ICC associated in this thesis appeared to be null this finding may be due to a dilution of effect by ACs.

These analyses also contribute new evidence regarding how long the increased risk of ICC associated with oral contraceptive use lasts after women stop using OCs. Although previous evidence suggests that the increase in risk wears off within 10 years of cessation of use,[6, 8] my research found a persistently elevated risk of invasive squamous cell cervical cancers, upto 30 years after last use of OCs.

In contrast, to the previous chapter, adjustment for screening history only slightly strengthened risk estimates for SCC and did not appreciably alter the associations for any other outcome.

9.2.5 Menopausal hormone therapy, screening and the risk of cervical neoplasia

The analyses in **Chapter 8** expanded those in the previous chapter on OCs and cervical neoplasia risk, by exploring the association between other exogenous hormones i.e., menopausal hormones and the risk cervical neoplasia, for which the evidence is extremely limited. These analyses show some evidence of a protective effect for the use of MHT and the risk of overall ICC, but there was no association with the risk of CIN3. There was again significant heterogeneity in the associations with MHT and the risk of ICC by histological tumour type. However, in contrast to the previous chapter, use of exogenous hormones in the form of MHT was associated with a 20% reduction in risk of SCC, but a non-significant increase in risk of AC although it is possible this analysis was under-powered. Nonetheless, these results are also in line with the hypothesis of different aetiologies for SCC and AC i.e., there is some suggestion of a potentially different degree of hormone responsiveness to the different components of hormone therapy between AC vs. SCC.[61]

The results also demonstrated that the risk associated with MHT was slightly attenuated by previous screening history but remained significant.

9.3 Possible mechanisms

Chapter 4 of this thesis showed differences in attendance for screening by personal factors. The findings of socio-demographic and behavioural factors may have a range of explanations, discussed in detail in **Section 4.3.4.2**, including perception of risks level of access to screening, level of endorsement of healthy behaviour and attitudinal factors such as fear. For reproductive and hormonal factors, there is the possibility that higher contact with health care systems via obstetric care and filling of prescriptions may influence attendance and/or frequency of attendance as women may be more likely to receive reminders for cervical screening.

In **Chapter 5**, women who did not attend for screening were more likely to develop ICC as they did not have the opportunity for the detection and treatment of precursor lesions via screening. The lack of association with AC may be due to the difficulty in sampling these cancers and their precursors using conventional screening techniques, as has been reported previously.[98, 190] Results showing a persistently high risk after previous abnormality are suggestive of the presence of persistent oncogenic HPV infection and may suggest that these women may have some underlying higher risks — perhaps for a number of reasons. First, to have a persistent infection or to develop precursor lesions, these women were exposed to HPV at least once, and therefore may have been at risk of being exposed to HPV again potentially via high-risk sexual behaviour, even if initial infection was transient or lesions were treated. However, there is also the possibility that these women have some inherent susceptibility to persistent HPV and/or the development of precursor lesiosn i.e., higher underlying risks.

In **Chapter 6**, after reciprocal adjustment, although an independent effect was seen for age at first FTP, there was no clear evidence of an association between number of FTPs and risk of ICC. This may be explained by the strong correlation between age at first FTP and sexual behaviour namely age at first sexual intercourse. As discussed in detail in **Chapter 6**, age at first sexual intercourse may underlie

observed associations with age at first FTP in addition to possible biological mechanisms as in subsequent chapters.

Findings in **Chapters 7-8** show some suggestion that sex steroid hormones, and particularly oestrogen, may influence the the risk of cervical cancer as discussed in detail in each respective chapter. There is growing evidence to suggest that cervical ACs represent a heterogeneous group of tumours with different aetiologies[61]. The findings here show some support to the notion of disparate origins of these cervical cancer histotypes, and warrant further investigation to elucidate potential biological mechanisms. It may be that the influence of oestrogen promotes carcinogenic events (as in **Chapters 6 and 7**), but oestrogen may also be involved in suppressing carcinogenesis (**Chapter 8**) and further work remains to be done to understand potential mechanisms.

9.4 Public health implications

The main epidemiological findings presented in this thesis constitute an important contribution to the literature both on cervical screening and the aetiology of cervical neoplastic disease.

Well-organised national screening programmes like that in the UK have successfully used cervical cytology to identify women at increased risk, and by treating pre-invasive precursors, have reduced the incidence and mortality of ICC in screened women.[54] In birth cohorts not vaccinated against HPV such as the Million Women Study (MWS) population, high screening coverage i.e., high attendance of eligible persons is key to maintaining the effectiveness of the screening programme.[17] However, latest figures show that nearly 30% of UK women do not take up the offer for cervical screening and little is known about the characteristics of women not attending for screening.[287] To increase screening participation, it is important to understand characteristics of the non-attenders, as demonstrated in this thesis. These findings are particularly important in light of new evidence that if offered a choice of screening, around half of women in England may

choose self-sampling.[288] Self-sampling for HPV i.e., HPV testing through self-collected specimens, is generally targeted to screening non-attenders in the context of organised screening programmes, has been shown to increase uptake among these women[289–291] and is now offered as part of routine screening in Australia, Denmark and the Netherlands.[292–294] Targeted identification of non-attenders may therefore improve distribution of self-sampling kits being trialled in England for integration into the NHSCSP.[295]

This thesis has shown some evidence of increased risks of cervical neoplasia associated with early age at first FTP even after allowance for multiparity. Further, risks associated with multi-parity and early age at first FTP when compared to nulliparous women were strengthened when adjusted for screening history. Although any true associations may be of little relevance in the U.K., where multiparity and early age at first birth are relatively uncommon,[296, 297] they have major public health implications in areas of the world where women have 3 or more children and begin childbearing at younger ages such as Sub-Saharan Africa.[298, 299] Future studies examining associations within these populations with a wider range of age at first birth/parity are therefore much needed. As HPV vaccination is also relatively inaccessible[300] and cervical cancer is more common in these countries,[262] using this evidence to offer targeted screening in these high-risk populations may be another strategy adopted as part of cervical cancer control programmes.

The findings from this thesis also suggest that the excess risks of cervical cancer associated with use of OCs persist for far longer than previously reported by the Collaboration.[6] The Collaboration results showed the risk of SCC declined with cessation of use until by 10 or more years since last use there was no significant increase in relative risk per year of use.[8] This thesis has shown evidence of a significant risk trend with increasing duration of use for invasive cervical tumours of squamous morphology, upto 30 years after cessation of use of OCs. This finding is particularly important for older women who would have used contraceptives over the course of their reproductive years who are no longer eligible for screening. Importantly, women in this age group would also have not received vaccination

against HPV which was first licensed for use in 2006 [301] and in the U.K. was only offered in 2008 to young girls aged 12-13 years and a catch-up service offered to girls aged up to 18 years.[79] Currently, there is little consensus about the age at which cervical screening should stop, and minimal evidence about the risk of cervical cancer in older women who are no longer eligible for screening.[302, 303] Although further studies on the balance of risks versus harms are required, this thesis provides some evidence that it may be appropriate to revise the upper age for cervical screening eligibility particularly for women who may be at higher risk of disease such as previously long-term users of OCs.

Finally, it is particularly important to have reliable epidemiological evidence of histotype-specific associations for cervical cancer at this time because in many countries worldwide whilst there is a trend of decreasing incidence of SCC,[120] there is also a relative and absolute increase in the incidence of AC (which currently accounts for 20% of all ICC in many populations).[97, 261, 304] There is therefore need to understand the aetiology of this histotype for continued cervical cancer prevention.[305] As mentioned in **Chapter 7, Section 7.3.4.3**, there is growing evidence to suggest that cervical adenocarcinomas represent a heterogeneous group of tumours with different aetiologies.[61] This thesis has shown some differences between AC and SCC with regard to hormone use consistent with this hypothesis. Given the difficulty in sampling adenocarcinomas via conventional screening methods, further work to understand aetiology of these cancers is particularly important at this time.

9.5 Strengths and limitations

As discussed in previous chapters, this thesis has many strengths including the linkage to screening data, which allowed the assessment of the confounding effect of previous screening history not previously possible; its prospective design, which helped minimise differential recall of certain exposure history amongst women with and without cancer, specifically OC or MHT use (a potential weakness of studies with retrospective assessment of exposures); the virtually complete follow-up and ascertainment of incident CIN3 and ICC over almost two decades, allowing for

the study of long-term risks; and the large size of the cohort, making possible analyses by histo-type.

This work in this thesis is, however, not without limitations. First, an obvious limitation is the lack of a measure of HPV status for this cohort. To mitigate this, this thesis has adjusted for screening history, including previous abnormalities which are likely to be a good proxy for persistent HPV infection.[231] There is also some uncertainty in the literature on how to account for HPV status in analyses, as discussed in **Chapter 3, Section 3.2.3.2** and the adjustment for screening history used in this thesis may well also go some way toward accounting for HPV status.

The lack of measures of sexual behaviour, which are known to be strongly associated with cervical neoplasia, is another potential limitation of the data used for analyses in this thesis. To mitigate any potential confounding by sexual behaviour, this thesis has adjusted for age at first FTP in all analyses. This is expected to be reasonable because, as discussed in **Chapter 6** on reproductive factors, the gap between the age people start having sex and the age they have their first child has widened over time.[306] For women in this cohort born around 1935-1950,[129] who would have had a short latency between age at first sexual intercourse and age at first pregnancy/child birth, age at first FTP as used in these analyses has been shown to be a good proxy for sexual initiation.[246, 247] In my analyses, adjustment for age at first FTP also attenuated relative risks of cervical neoplasia associated with parity (see **Chapter 6, Figures 6.1-6.3**). By contrast, risks associated with age at first FTP were largely unaffected by controlling for the number of FTPs. This large effect of the adjustment for age at first FTP has also been shown previously, and supports the notion that adjustment for age at first FTP in place of age at first sexual intercourse may be reasonable. [7] Early sexual initiation may also be a proxy for early HPV exposure and consequently potential confounding by HPV. However, it is expected that adjusting for previous screening test results should go some way toward adjusting for HPV exposure. Nonetheless, this thesis did not have information on other relevant aspects of sexual behaviour such as number of sexual partners and residual confounding by sexual

history cannot be completely ruled out, but the consistency of the associations seen with each reproductive and hormonal co-factor, in comparison to previous evidence, strongly supports the existence of real associations.

It is also important to note that the screening history period investigated in these analyses (1996-max 2001) is of a historic nature and analyses are also based on older women (aged 56 years on average at recruitment in 1996-2001). Therefore, findings from this thesis may be viewed as having limited relevance to current HPV-based screening and to screening in HPV vaccinated populations. However, these analyses were intended to inform on potential confounding by screening history in relation to cervical cancer aetiology, and have presented new evidence on the aetiology of histo-types squamous cell and adenocarcinoma. Future research may, however, consider providing prospective evidence on relevant risk factors e.g. oral contraceptive use and reproductive factors in cohorts recruiting younger women within the eligible age range for screening which this thesis does not address. Linkage to HPV-based screening data in these studies would also be useful in determining whether these associations are changed. The lack of screening data during follow-up may also influence results, with some mis-classification of screening attendance status in these results However, as past attendance has been shown to predict future attendance,[140] it is expected that any misclassification would be minimal.

These analyses are also subject to other more general limitations. Because women in the MWS were recruited to the study via a screening programme, there is possibly some selection bias in our participants who may be representative of women who attend for (breast) screening.[129] However, due to the large number of study participants in the dataset used for this thesis it is expected that the internal validity in the assessment of risk factors is not undermined by bias. Information on screening invitations to the NHS Cervical Screening Programme was also not available, but based on data from NHS performance audits of the screening programme during the screening history period for this thesis' analyses, it is unlikely that women were not invited.[101, 179] My research may also be subject to errors in routine registry coding systems as well as screening records, but any misclassification is

likely to be at random. Finally, as previously mentioned, numbers were too limited to carry out more stratified analyses such as analyses investigating the associations between menopausal hormone duration and recency of use and cervical cancer risk by histological tumour type.

9.6 Recommendations for future research

There are several areas for future research that follow from the work presented in this thesis. First, this thesis quantitatively demonstrates characteristics of non-attenders which may allow for targeted identification of non-attenders towards improving attendance for screening programmes. This research however may be expanded to incorporate qualitative research to provide a baseline understanding of the participant/non-participant perspective on attendance for screening. Augmenting these data in this way may provide an avenue to answer questions that may not be easily answered by quantitative methods.

Second, the Collaboration has shown that current smoking is associated with an increase risk of invasive SCC, but not of AC with significant heterogeneity between the two histotypes.[8] This investigation, like others,[158, 161] has shown differences in attendance for cervical screening by smoking status with current smokers more likely to, and past smokers less likely to not attend for screening. The current data-set i.e. the MWS cohort with linked NHSCSP records has detailed information on smoking history for all participants. This dataset could therefore be used to further expand our knowledge on the potential confounding effects of screening history in relation to the association between smoking and the risk of cervical neoplasia i.e., CIN3 and ICC including separately by histo-type.

More epidemiologic research with appropriately measured HPV status is needed to adequately rule out residual confounding by HPV. Most cohorts have not had HPV status due to the invasive nature of sampling,[307] however, these data may become more readily available in future with linkage to HPV-based routine screening data. Routine HPV-screening data will also allow for the inclusion of women with at least two consecutive HPV-positive smears over time to confirm

HPV persistence, which would avoid some of the limitations in interpretation of previous studies i.e. the inclusion of HPV measured at one point in time which may be transient. (see **Chapter 3 Section 3.2.3.2**) Alternatively, future work may include serological markers of HPV which have been suggested to be of value as a marker of cumulative lifetime exposure.[308]

With regard to potential confounding by sexual behaviour, information on sexual behaviour is now available in other large cohort studies and further work can be done to explore the extent of residual confounding by this factor. For example, data from the UK Biobank (UKB) is now available for around 46,000 MWS participants and includes information on sexual history including age at first sexual intercourse and lifetime number of sexual partners.[309] As information has been collected in the MWS about living with a partner, but not on lifetime number of sexual partners, these data can be used to 1) assess the value of using living with a partner as an indicator for sexual history to reduce the potential for this complex confounding within the joint UKB/MWS dataset of 46,000 women; and 2) assess the associations of sexual behaviour with reproductive and hormonal factors and screening history if the entire UK Biobank dataset is linked to screening data.

In this thesis, there was evidence of heterogeneity in the associations with exogenous hormones by histological tumour type, therefore, of particular interest would be future analyses on these cancers i.e. SCC and AC. Given that the early detection of adenocarcinomas via conventional screening methods is challenging, future studies should verify or refute the findings from this thesis in order to enhance our understanding of these cancers towards prevention efforts. Further work is also needed to clarify the role of OC use and MHT use in relation to type of hormones, concentrations, duration, recency, and latency by histological tumour type. Biological research to understand the mechanisms underlying associations on the influence of hormones would also be another area for further research. Such studies would be valuable in strengthening the biologic plausibility of the epidemiologic associations.

Finally, the work done involved analyses of data that are relevant to England. During the course of my DPhil., I have used some of the expertise gained over the course of my DPhil to plan a new study I would like to do in Kenya which is included in **Appendix G**. This project seeks to evaluate the quality of registration of female reproductive cancers, specifically breast, cervical, endometrial and ovarian cancers, in an urban population-based registry in Kenya, the Nairobi Cancer Registry (NCR). To my knowledge, this is the first comprehensive evaluation of the data quality at the NCR from three different aspects: comparability, completeness and validity using methods described by Parkin and Bray.[310] The information provided by cancer registries are the basis for epidemiological cancer research and it is important that statistics reported (incidence and survival) are as close to true values as possible. Regular evaluation of the registry is a quality control procedure underpinning its value and its ability to carry out its functions including description of cancer patterns, care, outcomes, and follow-up of these variables in relation to control activities such as the monitoring and evaluation of cancer screening. For example, it is anticipated that this project may form the outcome assessment as part of a wider project towards developing linkage to cancer screening data-sets in Sub-Saharan Africa. The linkage of screening data-sets, in turn, provides the opportunity to quantify the (unmet) need for cancer screening and to potentially identify high-risk groups for targeted intervention. In order to carry out this project, I have been able to secure grant funding of £1000 pounds (see **Appendix G Figure G.2**) to enable me to access the Nairobi Cancer Registry and will continue the work upon my return to Kenya after the DPhil.

9.7 Conclusion

Cervical cancer remains a substantial health problem for women globally, requiring more effective prevention and control strategies. Targeted interventions should be offered to increase access to cervical cancer screening for women not participating in routine screening. These findings are also consistent with the notion that at

least a subset of adenocarcinomas may have different aetiologies and demonstrate the considerable potential for future research on these cancers.

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Appendices

A

The Million Women Study, NHS Cervical Screening Programme records & Methods

A.1 Million Women Study Recruitment Questionnaire

This questionnaire was completed by study participants at recruitment, in 1996-2001. I had no role in developing the questionnaire.

THE MILLION WOMEN STUDY

A national survey of women invited for breast screening

We need one million women to help us in research that will benefit women all over the world.
Would you become one of these special women?

More and more women are taking hormone replacement therapy (HRT) so it is vital that we find out as much as possible about its benefits and any possible side effects. We have a unique opportunity through the NHS Breast Screening Programme to learn about the way different types of HRT and other lifestyle factors affect a woman's health, particularly her breasts. Britain is the only country in the world that can carry out this study because it is the only one with the combination of a large population and a comprehensive national breast screening programme.

The NHS Breast Screening Programme, the Imperial Cancer Research Fund and the Medical Research Council have joined together to organise The Million Women Study. If one million women answer this questionnaire over the next three years we could have some of the answers to our most important questions about HRT within five years or so.

We would be very grateful if you could set aside some time to answer these questions. It should not take more than 10-15 minutes. You do not have to answer this questionnaire and if you decide not to you will still have your screening done in the normal way.

Please answer every question and do not leave blanks as all the information that you give us is very useful. If you are not sure about exact dates or ages an approximate answer is better than none. If you have any questions you can ring us on freephone **0800 262 872.**

Even if you are not taking HRT it is just as important that you fill in the questionnaire.
Please bring this questionnaire to your breast screening appointment

To help us read your answers please write as clearly as possible and be sure to complete the questionnaire as shown:
Please put a cross in the appropriate box(es) ☒ ☐ ☐

OR put numbers in the appropriate box e.g. *23rd April 1946* 2 3 / 0 4 / 4 6 *age* 4 4 *years*

SAMPLE

GENERAL QUESTIONS ABOUT YOU

1. What is your date of birth? *(please put day/month/year)*
☐☐ / ☐☐ / ☐☐

2. How old are you? ☐☐ years

3. How tall are you? *(please give to the nearest inch)*
☐ feet ☐☐ inches

4. About how much do you weigh?
☐☐ stone ☐☐ lbs

5. How old were you when you finished full time schooling? *(please cross one box)*
- ☐ did not go to school
- ☐ 13 or younger
- ☐ 14
- ☐ 15
- ☐ 16
- ☐ 17 or older

6. What qualification(s) do you have from school, college or the equivalent?
(please put a cross in the most appropriate box(es))
- ☐ clerical or commercial qualifications *(eg secretarial, hairdressing etc)*
- ☐ nursing or teaching
- ☐ "O" level *(or equivalent)*
- ☐ "A" level *(or equivalent)*
- ☐ college/university degree *(or equivalent)*
- ☐ none of these

7. About how many cigarettes do you smoke on average *each day*, now? *(please cross one box)*
- ☐ none
- ☐ less than 5
- ☐ 5-9
- ☐ 10-14
- ☐ 15-19
- ☐ 20-24
- ☐ 25 or more

8. Are you an ex-smoker? ☐ No ☐ Yes

9. About how much wine, beer or spirits do you drink on average *each week*? *(please cross one box for each type)*

Wine (glasses per week)	**Lager/Cider/Beer** (half pints per week)	**Spirits** (tots per week)
☐ none	☐ none	☐ none
☐ less than 1	☐ less than1	☐ less than1
☐ 1-3	☐ 1-3	☐ 1-3
☐ 4-6	☐ 4-6	☐ 4-6
☐ 7-10	☐ 7-10	☐ 7-10
☐ 11-15	☐ 11-15	☐ 11-15
☐ 16-20	☐ 16-20	☐ 16-20
☐ 21+	☐ 21+	☐ 21+

If you drink **wine** is it
- ☐ mostly red
- ☐ mostly white
- ☐ about the same amount of red and white?

10. How often do you do *any* exercise?

- ☐ rarely/never
- ☐ less than once a week
- ☐ once a week
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ every day

11. How often do you do *strenuous* exercise?

(that is, enough to cause sweating or a fast heart beat.)

- ☐ rarely/never
- ☐ less than once a week
- ☐ once a week
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ every day

QUESTIONS ABOUT YOU AND YOUR FAMILY

12. Have you ever had any children? ☐ No ☐ Yes

- if No, please go on to question 15

13. How many children have you had? ☐☐

(please include stillbirths; it is not necessary to include miscarriages)

14. When was each child born, and for how many months did you breastfeed each child, if at all?

	DATE OF BIRTH (If you had twins or triplets please repeat the same date for each child) day / month / year	BREASTFEEDING (Months that you breastfed each child; put "0" if you did not breastfeed that child at all; "1" if you breastfed for a month or less)
1st child	☐☐ / ☐☐ / ☐☐	☐☐ months
2nd child	☐☐ / ☐☐ / ☐☐	☐☐ months
3rd child	☐☐ / ☐☐ / ☐☐	☐☐ months
4th child	☐☐ / ☐☐ / ☐☐	☐☐ months
5th child	☐☐ / ☐☐ / ☐☐	☐☐ months
6th child	☐☐ / ☐☐ / ☐☐	☐☐ months
7th child	☐☐ / ☐☐ / ☐☐	☐☐ months
8th child	☐☐ / ☐☐ / ☐☐	☐☐ months
9th child	☐☐ / ☐☐ / ☐☐	☐☐ months
10th child	☐☐ / ☐☐ / ☐☐	☐☐ months

15. Have you ever been for breast screening before?

- ☐ No
- ☐ Yes- If **Yes**, about how many years ago was your last screen? ☐☐ years ago

16. Have you ever had a breast lump removed or any operations on your breast(s)?

- ☐ No
- ☐ Yes- If **Yes**, how old were you? ☐☐ years

(If you have had more than one operation please write your age at the first operation)

17. Have you ever had breast cancer diagnosed?

- ☐ No
- ☐ Yes- If **Yes**, how old were you when the cancer was first diagnosed? ☐☐ years

18. Has your mother ever had breast cancer diagnosed?

- ☐ No ☐ Don't know
- ☐ Yes- If **Yes**, how old was she when the cancer was first diagnosed? ☐☐ years

19. How many sisters do you have? ☐☐ sisters

(put"0" if you do not have any sisters, please include any sisters who have died)

20. Have any of your sisters ever had breast cancer diagnosed?

- ☐ No/No sisters ☐ Don't know
- ☐ Yes- If **Yes**, how old were they when the cancer was first diagnosed?

1st sister ☐☐ years **2nd sister** ☐☐ years

QUESTIONS ABOUT YOUR HEALTH

21. Have you ever had any other cancer?

☐ Yes ☐ No

Please describe

22. Have you EVER had:

(please cross "Yes" or "No" for each condition)

High blood pressure - when pregnant	☐ Yes	☐ No
High blood pressure - when not pregnant	☐ Yes	☐ No
Heart disease *(eg heart attack/angina)*	☐ Yes	☐ No
Stroke	☐ Yes	☐ No
Diabetes	☐ Yes	☐ No
High blood cholesterol	☐ Yes	☐ No
Blood clot *(thrombosis)*	☐ Yes	☐ No

23. Are you NOW being treated for:

High blood pressure *(hypertension)*	☐ Yes	☐ No
Heart disease	☐ Yes	☐ No
Diabetes	☐ Yes	☐ No
High blood cholesterol	☐ Yes	☐ No
Varicose veins	☐ Yes	☐ No
Clotting problems	☐ Yes	☐ No
Asthma	☐ Yes	☐ No
Rheumatoid arthritis	☐ Yes	☐ No
Osteoarthritis	☐ Yes	☐ No
Thyroid problems	☐ Yes	☐ No
Osteoporosis	☐ Yes	☐ No
Depression/Anxiety	☐ Yes	☐ No

SAMPLE

24. Are you *NOW* being treated for any other *serious* illness?
☐ Yes ☐ No

Please describe this illness

Please describe the treatment

QUESTIONS ABOUT PAST OPERATIONS

25. Have you had a hysterectomy?
☐ No
☐ Yes- If **Yes**, how old were you? ☐☐ years

26. Have you had BOTH ovaries removed?
☐ No ☐ Not sure
☐ Yes- If **Yes**, how old were you? ☐☐ years

27. Have you been sterilised *(had your tubes tied)***?**
☐ No
☐ Yes- If **Yes**, how old were you? ☐☐ years

QUESTIONS ABOUT YOUR USE OF THE PILL

28. Have you ever used the pill *(oral contraceptive)*?
☐ Yes
☐ No **- *if No, please go to question 32***

29. About how old were you when you *first went on* the pill? ☐☐ years

30. About how old were you when you *last came off* the pill? ☐☐ years

31. For how many years *in total* did you take the pill?
☐☐ years

(Add together the years and months when you actually took the pill -do not count the years and months when you were not taking it. Please write "0" if you used the pill for less than a year in total)

QUESTIONS ABOUT YOUR USE OF HORMONE REPLACEMENT THERAPY (HRT)

32. Have you ever used hormone replacement therapy (HRT)? ☐ No **- *if No - please go to question 39***
☐ Yes

33. How old were you when you *first started* using HRT?
☐☐ years

34. Had your periods stopped before you started using HRT? *(Cross "Yes" if you had a hysterectomy before starting HRT)*
☐ No
☐ Yes **- if Yes**, how old were you when your periods stopped? ☐☐ years

35. For about how many years *in total* have you used HRT? ☐☐ years

(Add together the years and months when you used HRT - do not count the years and months when you were not using HRT. Please write "0" if you used HRT for less than a year in total)

36. Are you *now* using HRT?
☐ Yes
☐ No **- if No**, how old were you when you **last** used HRT? ☐☐ years

37. What is the name of the most RECENT HRT you have used?

☐ Prempak C 0.625mg	☐ Premarin 0.625mg
☐ Prempak C 1.25mg	☐ Premarin 1.25mg
☐ Tridestra	☐ Evorel 25mcg/50mcg
☐ Trisequens	☐ Evorel 75mcg/100mcg
☐ Trisequens Forte	☐ Progynova 1mg
☐ Cycloprogynova 1mg	☐ Progynova 2mg
☐ Cycloprogynova 2mg	☐ Estraderm 25mcg
☐ Estrapak	☐ Estraderm 50mcg
☐ Estracombi	☐ Estraderm 100mcg
☐ Climaval 1mg	☐ Zumenon 1mg
☐ Climaval 2mg	☐ Zumenon 2mg
☐ Premique Cycle	☐ Ethinyloestradiol
☐ Premique	☐ Micronor
☐ Nuvelle	☐ Provera
☐ Kliofem	☐ Duphaston
☐ Livial	

☐ Do not know ☐ Implants ☐ Oestrogel

Other *(please write here)*

38. For how many years in total did you use the most *recent* type of HRT? ☐☐ years

(Please write "0" if you used this recent HRT for less than a year in total)

SAMPLE

QUESTIONS ABOUT YOUR PERIODS

39. About how old were you when your periods started? ☐☐ years

40. Have your periods NOW stopped?

*Cross "**Yes**"-if you are not having periods now, either because of your menopause, after a hysterectomy or after stopping HRT.*
*Cross "**No**"- if you are still having regular periods now, even if they are because you are taking HRT.*
*Cross "**Irregular**"-if your periods have been irregular and you think it might be because of the menopause.*

☐ **Yes**- If **Yes**, how old were you when they **stopped**? ☐☐ years

☐ **No**

☐ **Irregular**

FINAL SECTION

41. So that we can find out about your health in the future we may need to contact you again or look at your screening or medical records. We would be grateful if you gave us permission to contact you again or to use information from those records. **We guarantee that all information obtained will be treated with absolute confidentiality and used for medical research only.** Of course, you do not have to give permission. Your response to this request will not affect your screening or the treatment you receive in any way.

If you give permission, please sign here and print your name, address and other details in the section below. Please print in BLOCK CAPITALS as clearly as possible.

Signature: ☐ today's date: ☐☐ ☐☐ ☐☐

Surname: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Given name(s): ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

House number and street: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

District: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Town: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

County: ☐☐☐☐☐☐☐☐☐☐ Postcode: ☐☐☐☐☐☐☐☐

Surname at birth: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Town of birth: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

NHS (National Health Service)Number: ☐☐☐☐☐☐☐☐☐☐
(The number on your medical card)

Breast Screening Number: ☐☐☐☐☐☐☐☐☐☐
*(This is in the top left hand corner of your **screening invitation letter** and starts with the letters LGL)*

SAMPLE

Please bring this questionnaire to your breast screening appointment

If you would like to post this questionnaire back to us, please send it to:
THE MILLION WOMEN STUDY CO-ORDINATING CENTRE
ICRF-CEU, GIBSON BUILDING,
RADCLIFFE INFIRMARY,
OXFORD OX2 6HE

FREEPHONE: 0800 262 872

Breast Screening Unit
Linton House
Thirlestaine Road
Cheltenham
GL53 7AS

LGL ☐

THANK YOU VERY MUCH FOR YOUR HELP

B

Personal factors affecting non-attendance for organised cervical screening

B.1 Literature Review

Publication	Region	Population	Exclusion criteria	Age range, years	n	Screening history assessment; Non-attender definition	% Non-attenders	Response rate %	OUTCOME ESTIMATE OF NON-ATTENDANCE OR* (95% CI)								Adjustments
									Sociodemographic			Behavioural		Reproductive		Hormonal		
									Age	SES	Education	Smoking	BMI	Parity	Age at first FTP	OC use	MHT use	
Hansen et al.,2011[160]	Norway	Non-specific	Age <25 years, wrong PIN, opt out of NCCSP reminders, history of cervix removal, history of gynaecological cancer	25-45	12,058	NCCSP records; No Pap smear recorded in the last 4 years	13.4	68	1.00 (0.80, 1.25) for ages 40+ vs 25-29 years	—	1.23 (1.04-1.45) for 13-16 vs 16+ years of education	1.41 (1.20-166) for current vs. never smokers; 0.94 (0.78-1.13) for former vs. never smokers.	—	1.70 (1.28-2.27) for 0 vs. 3+ births	—	0.47 (0.39-0.57) for ever vs. never users	—	Age, education, marital status, self-rated health, smoking, wine drinking, number of sex partners, age at first coitus, ever had STI, ever pregnant, number of births, OC use, OC use in the last month, ever use condoms, awareness factors
Kristensson et al.,2014[153]	Denmark	Non-specific	History of hysterectomy	25-54	1,052,447	Pathology databank; No cervical cytology test during 5-year follow-up	17.4	—	1.98 (1.95-2.02) for age 50-54 vs 25-29 years	—	1.11 (1.09-1.14) for secretarial sales vs academics	—	—	—	—	—	—	Age, civil status, nationality, education, hospitalisation and contact with GPs, specialists and dental services
Leinonen et al., 2017[157] [a]	Norway	Non-specific	Previous diagnosis of gynaecological cancer	25-69	1,309,679	NCCSP records; No screening test[b] in study period	34.0	—	—	PR 0.83 (0.82-0.85) for highest (Q5) vs lowest quintile of income (Q1)	PR 1.18 (1.16-1.19) for primary vs university	—-	—-	PR 1.04 (1.03-1.06) for women with 0 vs. 4+ births	—	—	—	Woman's origin, marital status, parity, region of residence, education, occupation, employment, annual income
Idehen et al.,[156]	Finland	Russian immigrants	—-	18-64	284	Self-report; No participation in any screening including Pap tests within the past 5 years	—	29.1	0.90 (0.85-0.98) per single year increase in age	0.61 (0.47-1.37) for employed vs. housewife	—	—	—	0.96 (0.28-3.30) for never vs. ever given birth	—	—	—	Age, literacy in Finnish, marital status, number of family members, employment status, age of migration, experienced discrimination, general health check-up, parity
		Somali immigrants	—-	18-64	98	Self-report; No participation in any screening including Pap tests within the past 5 years	—	13.2	0.94 (0.88-1.01) per single year increase in age	—	—	—	—	—	—	—	—	Age, literacy in Finnish, living outside metropolitan area, gynaecological check-up, distrust in public health care service, FGM
		Kurdish immigrants	—	18-64	191	Self-report; No participation in any screening including Pap tests within the past 5 years	—	19.7	0.98 (0.93-1.02) per single year increase in age	0.23 (0.08-0.67) for employed vs. housewife	2.63 (1.23-5.88) for no education vs. high school education	—	—	10.00 (1.58-50.00) for never vs. ever given birth	—	—	—	Age, education, marital status, number of family members, employment status, living outside metropolitan area, gynaecological check-up, self-rated health, parity
Møen et al., 2017[154]	Norway	Non-specific	—	25-69	1,321,632	Norwegian Health Economics Administration Database; No consultations with diagnoses related to screening for cervical cancer[a]	92.6	—	1.33 (1.30-1.35) for ages 56-75 vs. 25-40 years	0.86 (0.85-0.87) for high vs. low income[b]	—	—	—	—	—	—	—	Age, region of origin, marital status, income, municipality centrality, GP's sex and immigrant background
Chang et al., 2017[155] [a]	Korea	Non-specific	Incomplete responses on weight, height or screening, women aged 40+ years, girls aged <15 years old and men	15-40	3734	Self-report; No cervical screening, including Pap smear within the past 2 years	53.6	80%	0.91 (0.87-0.95) per year increase in age	0.47 (0.26-0.84) for highest vs. lowest quartile income	3.70 (0.88-16.67) for <6 vs. 12+ years of education	1.41 (0.96-2.09) for current vs never smokers; 0.83 (0.52-1.32) for ex vs never smokers	—	—	—	—	—	Age, education, total house income, smoking status, drinking frequency and job status.
Harder et al.,2018[158]	Denmark	Non-specific	History of hysterectomy, missing information	23-64	476,670	Pathology Databank screening records; Neither actively unsubscribed from screening nor had cervical cytology registered during 4-year follow-up	15.5	—	—	0.30 (0.28- 0.32) for income DKK 231,400+ vs. DKK <1	2.56 (2.43-2.63) for basic education vs. high education[a]	—	1.16 (1.13-1.20) for ever vs. never obese[b]	1.21 (1.18-1.23) for 0 vs. 1 live birth; 0.73 (0.66-0.84) for 0 vs 4+live births	—	—	—	Age, country of origin, marital status, educational level and income
Hertzum-Larsen et al., 2019 [159]	Denmark	Western and Non-Western immigrants[a]	Second-generation immigrants, non-Danish born descendants, unknown country of origin, non-residents, unsubscribed from screening, hysterectomised, pregnant women, invitation letters returned to sender, missing sociodemographic data	23-64	610, 907	Pathology databank; No cervical screen within 2.9 years after invitation	39.1, 39.3[b] -	—	0.74 (0.69-0.80) for Q4 annual incomed vs. Q1 in Western immigrants; 0.76 (0.73-0.80) for Q4 annual income[d] vs. Q1 Non-Western immigrants	—	—	—	—	1.38 (0.97-2.00) for 0 vs. 4+ live births in Western immigrants; 0.71 (0.63-0.78) for 0 vs. 4+ live births in Non-Western immigrants	—	—	—	Age, employment status, income and civil status
Harder et al., 2020[161]	Denmark	Non-specific	Prior cancer, abnormal cervical cytology or histology, emigration, death during follow up and missing sociodemographic information	23-64	14,271	Pathology databank; No cervical cytology registered within 4-year follow-up	13.9	75%	—	—	—	1.81 (1.61-2.03) for daily vs. no current smoking	1.46 (1.27-1.67) for obese vs. normal weight	—	—	—	—	Age, marital status, education, employment, income country of origin

Table B.1: Studies published on personal factors influencing non-attendance to organised screening programmes

Abbreviations: YOP- year of publication, n-number, y-years, OR- odds ratio, PR- prevalence ratio, CI-confidence interval, SES-socioeconomic status, DKK- Danish krone, BMI-body mass index, OC- oral contraceptives, MHT -menopausal hormone therapy, STI- sexually transmitted infection, AFSI- age at first sexual intercourse, NCCSP-Norwegian Coordinated Cytology Screening Programme

* unless otherwise specified

B.2 Sensitivity Analyses

B.2.1 Analyses restricted to women with data for all variables

	No. of non-attenders/attenders	OR for non-attendance vs. attendance		No. of attenders >5/≤5 years before baseline	OR for attendance >5/≤5 years before baseline	
		Minimally adjusted±	Fully adjusted (95% CI)		Minimally adjusted±	Fully adjusted (95% CI)
Age at baseline, years						
<55	7808/362 918	1.00	1.00 (–)	14 682/348 236	1.00	1.00 (–)
55-60	5898/223 038	1.23	1.13 (1.09, 1.17)	10 145/212 893	1.13	1.15 (1.12, 1.18)
60-64	7197/182 651	1.83	1.31 (1.26, 1.36)	11 036/171 615	1.52	1.39 (1.35, 1.43)
			Het. χ^2_2=220.8 (p<0.001)			Het. χ^2_2= 560.2 (p<0.001)
Deprivation tertile						
Least deprived,1	5805/264 616	1.00	1.00 (–)	10 802/253 814	1.00	1.00 (–)
2	7027/261 194	1.21	1.16 (1.12, 1.20)	11978/249 216	1.11	1.07 (1.05, 1.10)
Most deprived, 3	8071/242 797	1.50	1.41 (1.36, 1.46)	13 083/229 714	1.34	1.22 (1.18, 1.25)
			Het. χ^2_2= 347.2 (p<0.001)			Het. χ^2_2= 202.9 (p<0.001)
Educational qualifications						
None	8923/324 498	1.00	1.00 (–)	15 814/308 684	1.00	1.00 (–)
Technical	3177/124 570	0.94	1.03 (0.99, 1.07)	5544/119 026	0.92	1.02 (0.99, 1.06)
Secondary	5261/213 227	0.94	1.05 (1.02, 1.09)	9544/203 683	0.93	1.07 (1.04, 1.10)
Tertiary	3542/106 312	1.27	1.29 (1.23, 1.34)	4961/101 351	0.99	1.13 (1.09, 1.17)
			Het. χ^2_3=131.6 (p<0.001)			Het. χ^2_3=58.6 (p<0.001)
Body mass index, kg/m^2						
<25	9182/374 853	1.00	1.00 (–)	15 249/359 604	1.00	1.00 (–)
25-29	6950/265 852	1.05	1.11 (1.07, 1.14)	12 369/253 483	1.14	1.16 (1.13, 1.19)
30+	4771/127 902	1.50	1.46 (1.41, 1.52)	8245/119 657	1.62	1.60 (1.55, 1.64)
			Het. χ^2_2= 383.6 (p<0.001)			Het. χ^2_2 1007.1 (p<0.001)
Smoking status						
Never	11 372/380 885	1.00	1.00 (–)	16 970/363 915	1.00	1.00 (–)
Past	5436/243 478	0.75	0.85 (0.82, 0.88)	10148/233 330	0.94	0.97 (0.95, 1.00)
Current	4095/144 244	1.00	1.22 (1.17, 1.27)	8745/135 499	1.44	1.56 (1.52 1.61)
			Het. χ^2_2= 266.8 (p<0.001)			Het. χ^2_2=1134.9 (p<0.001)
Past oral contraceptive use						
Never	14 321/294 101	1.00	1.00 (–)	17 118/276 983	1.00	1.00 (–)
Ever	6582/474 506	0.30	0.42 (0.41, 0.43)	18 745/455 761	0.71	0.81 (0.79, 0.83)
			Het. χ^2_1= 2929.8 (p<0.001)			Het. χ^2_1= 318.1 (p<0.001)
Menopausal hormone therapy use						
Never	17 244/423 984	1.00	1.00 (–)	25 623/398 361	1.00	1.00 (–)
Ever	3659/344 623	0.27	0.30 (0.29, 0.32)	10 240/334 383	0.48	0.50 (0.48, 0.51)
			Het. χ^2_1= 4840.8 (p<0.001)			Het. χ^2_1= 3589.9 (p<0.001)
Parity						
Parous	10 720/688 070	1.00	1.00 (–)	28 831/659 239	1.00	1.00 (–)
Nulliparous	10 183/80 537	8.14	7.19 (6.99, 7.41)	7032/73 505	2.19	2.18 (2.12, 2.24)
			Het. χ^2_1= 15741.4 (p<0.001)			Het. χ^2_1= 2644.6 (p<0.001)
In parous women: *						
Number of FTPs						
1-2	6641/442 399	1.00	1.00 (–)	73 505/424 995	1.00	1.00 (–)
3-4	3483/221 012	1.01	0.97 (0.94, 1.01)	17404/211 198	1.11	1.07 (1.04, 1.10)
5+	596/24 659	1.45	1.17 (1.07, 1.28)	9814/23 046	1.60	1.36 (1.28, 1.44)
			Het. χ^2_3=4.6 (p<0.001)			Het. χ^2_3=24.8 (p<0.001)
Age at first FTP, years						
<18	301/17 961	1.20	1.11 (1.00, 1.25)	856/17 105	1.25	1.09 (1.01, 1.17)
18-20	1795/115 442	1.06	1.04 (0.97, 1.09)	5035/110407	1.10	1.03 (0.99, 1.07)
21-24	3955/25 9561	1.00	1.00 (–)	10539/249022	1.00	1.00 (–)
25+	4365/279 561	1.02	1.03 (0.99, 1.08)	11 541/267 507	1.02	1.07 (1.04, 1.10)
			Het. χ^2_3=4.6 (p<0.001)			Het. χ^2_3=24.8 (p<0.001)

Table B.2: Odds ratios (95% CI) for non-attendance versus attendance and attendance >5 years vs. ≤5 years before recruitment for organised cervical screening according to personal factors for women with complete information

Abbreviations: OR, odds ratio; CI, confidence interval; FTPs, full-term pregnancies
±Minimally adjusted models were adjusted for age at recruitment, region of residence.
Fully adjusted models were additionally adjusted for deprivation tertiles, educational qualifications, body mass index, smoking status, oral contraceptive use, menopausal hormone therapy and in parous women age at first FTP or number of FTPs where appropriate.

B.2.2 Analyses comparing 5-year screening window to 3-year screening window

	No. of attenders >5/≤5 years before baseline	OR for attendance >5/≤5 years before baseline		No. of attenders >3/≤3 years before baseline	OR for attendance >3/≤3 years before baseline	
		Minimally adjusted±	Fully adjusted (95% CI)		Minimally adjusted±	Fully adjusted (95% CI)
Age at baseline, years						
<55	16 629/381 478	**1.00**	**1.00** (–)	88 987/309 102	1.00	1.00 (–)
55-60	11 558/235 124	1.13	1.14 (1.11, 1.17)	58 380/188 294	1.07	1.08 (1.06, 1.09)
60-64	12 658/192 390	1.51	1.37 (1.34, 1.41)	54 618/150 421	1.26	1.20 (1.19, 1.22))
			Het. χ^2_2=758.2 (p<0.001)			Het. χ^2_2= 541.2 (p<0.001)
Deprivation tertile						
Least deprived,1	611 918/274 489	**1.00**	**1.00** (–)	65 675/220 719	1.00	1.00 (–)
2	13 409/272 997	1.11	1.07 (1.05, 1.10)	69 476/216 919	1.03	1.01 (1.00, 1.02)
Most deprived, 3	15 518/261 506	1.36	1.23 (1.19, 1.26)	66 834/210 179	1.09	1.04 (1.02, 1.05)
			Het. χ^2_2= 33.6 (p<0.001)			Het. χ^2_2= 142.5 (p<0.001)
Educational qualifications						
None	16 844/321 678	**1.00**	**1.00** (–)	86 537/271 704	1.00	1.00 (–)
Technical	6058/126 928	0.91	1.03 (1.00, 1.06)	30 990/101 990	0.95	0.99 (0.98, 1.01)
Secondary	10 227/214 107	0.92	1.08 (1.05, 1.11)	53 072/171 253	0.95	1.00 (0.99, 1.02)
Tertiary	5307/106 933	0.97	1.13 (1.09, 1.17)	25 817/86 422	0.94	1.00 (0.98, 1.01
			Het. χ^2_3=5.7 (p<0.001)			Het. χ^2_3=33.5 (p<0.001)
Body mass index, kg/m^2						
<25	16 085/375 625	**1.00**	**1.00** (–)	88 671/303 026	1.00	1.00 (–)
25-29	13 105/266 375	1.13	1.16 (1.13, 1.18)	66 435/213 030	1.07	1.08 (1.06, 1.09)
30+	5159/135 437	1.51	1.46 (1.41, 1.52)	35 347/100 084	1.23	1.22 (1.20, 1.24)
			Het. χ^2_2 688.2 (p<0.001)			Het. χ^2_2= 601.3 (p<0.001)
Smoking status						
Never	18 778/393 203	**1.00**	**1.00** (–)	97 321/314 648	1.00	1.00 (–)
Past	11 560/257 456	0.94	0.97 (0.95, 1.00)	61 896/207 104	0.98	0.99 (0.98, 1.00)
Current	10174/152 402	1.45	1.55 (1.51 1.59)	41 211/121 358	1.16	1.19 (1.17, 1.20)
			Het. χ^2_2= 681.0 (p<0.001)			Het. χ^2_2=732.2 (p<0.001)
Oral contraceptive use						
Never	19357/305 604	**1.00**	**1.00** (–)	83 979/241967	1.00	1.00 (–)
Ever	20 960/495 064	0.72	0.82 (0.80, 0.84)	115 937/400 067	0.87	0.92 (0.91, 0.93)
			Het. χ^2_1= 218.8 (p<0.001)			Het. χ^2_1= 293.4 (p<0.001)
Menopausal hormone therapy use						
Never	28 862/436 862	**1.00**	**1.00** (–)	121 266/344 436	1.00	1.00 (–)
Ever	11 440/363 336	0.48	0.50 (0.49, 0.51)	78 244/296 519	0.75	0.76 (0.75, 0.77)
			Het. χ^2_1= 2657.3 (p<0.001)			Het. χ^2_1= 5354.3 (p<0.001)
Parity						
Parous	32 842/726 010	**1.00**	**1.00** (–)	176 259/582 561	1.00	1.00 (–)
Nulliparous	7804/79 966	2.16	2.15 (2.10, 2.21)	24 878/62 889	1.30	1.30 (1.28, 1.32)
			Het. χ^2_1= 997.8 (p<0.001)			Het. χ^2_1= 2321.9 (p<0.001)
In parous women:						
Number of FTPs						
1-2	82 982/463 842	**1.00**	**1.00** (–)	109 918/373 530	1.00	1.00 (–))
3-4	19 623/234 871	1.10	1.06 (1.04, 1.09)	58 543/187 548	1.05	1.03 (1.02, 1.05)
5+	11 234/27 297	1.62	1.35 (1.28, 1.42)	7798/21 483	1.22	1.13 (1.10, 1.16)
			Het. χ^2_2= 83.4 (p<0.001)			Het. χ^2_2= 30.2 (p<0.001)
Age at first FTP, years						
<18	992/19 357	1.23	1.07 (1.00, 1.15)	4821/15 527	1.06	1.01 (0.99, 1.04)
18-20	5864/123 797	1.11	1.03 (0.99, 1.06)	30 405/99 251	1.04	1.01 (1.00, 1.03)
21-24	11 995/274 159	**1.00**	**1.00** (–)	66 043/220 097	1.00	1.00 (–)
25+	12 877/290 136	1.01	1.07 (0.99, 1.10)	70 106/232 895	1.00	1.02 (1.01, 1.04)
			Het. χ^2_3=13.8 (p=0.003)			Het. χ^2_3=16.2 (p=0.001)

Table B.3: Odds ratios (95% CI) for attendance >5 years vs. ≤5 years before recruitment, and attendance >3 years versus attendance ≤3 years before baseline for organised cervical screening according to personal factors

Abbreviations: OR, odds ratio; CI, confidence interval; FTPs, full-term pregnancies
±Minimally adjusted models were adjusted for age at recruitment, region of residence.
Fully adjusted models were additionally adjusted for deprivation tertiles, educational qualifications, body mass index, smoking status, oral contraceptive use, menopausal hormone therapy and in parous women age at first FTP or number of FTPs where appropriate.

C

Screening history and the risk of cervical neoplasia

C.1 Results

C.1.1 Study Participants

	% (n) of women*			
	≤ 5 years before recruitment		**> 5 years before recruitment**	
	No abnormalities (n=712 785)	**Any abnormality (n=96 207)**	**No abnormalities (n=39 222)**	**Any abnormality (n=1623)**
Mean age at baseline (SD)	56.2 (4.4)	55.2 (4.1)	56.9 (4.6)	56.9 (4.6)
Most deprived tertile	32 (227 820)	34 (30 756)	38 (14 841)	39 (611)
No educational qualifications	2 (16 494)	2 (1938)	3 (1082)	3 (39)
Body mass index 30+kg/m^2	17 (112 066)	16 (13 586)	23 (8442)	23 (336)
Current smokers	19 (131 313)	20 (18 567)	25 (9663)	29 (454)
Ever oral contraceptive use	61 (429 551)	67 (60 382)	52 (19 995)	56 (876)
Ever menopausal hormone therapy use	45 (314 005)	51 (45 963)	28 (10 921)	31 (490)
Nulliparous	10 (73 013)	7 (6353)	19 (7595)	13 (199)
Among parous women:				
Mean number of births (SD)	2.1 (1.2)	2.3 (1.2)	2.0 (1.5)	2.0 (1.5)
Age at first birth <18 years	3 (16 265)	3 (2761)	3 (928)	4 (55)

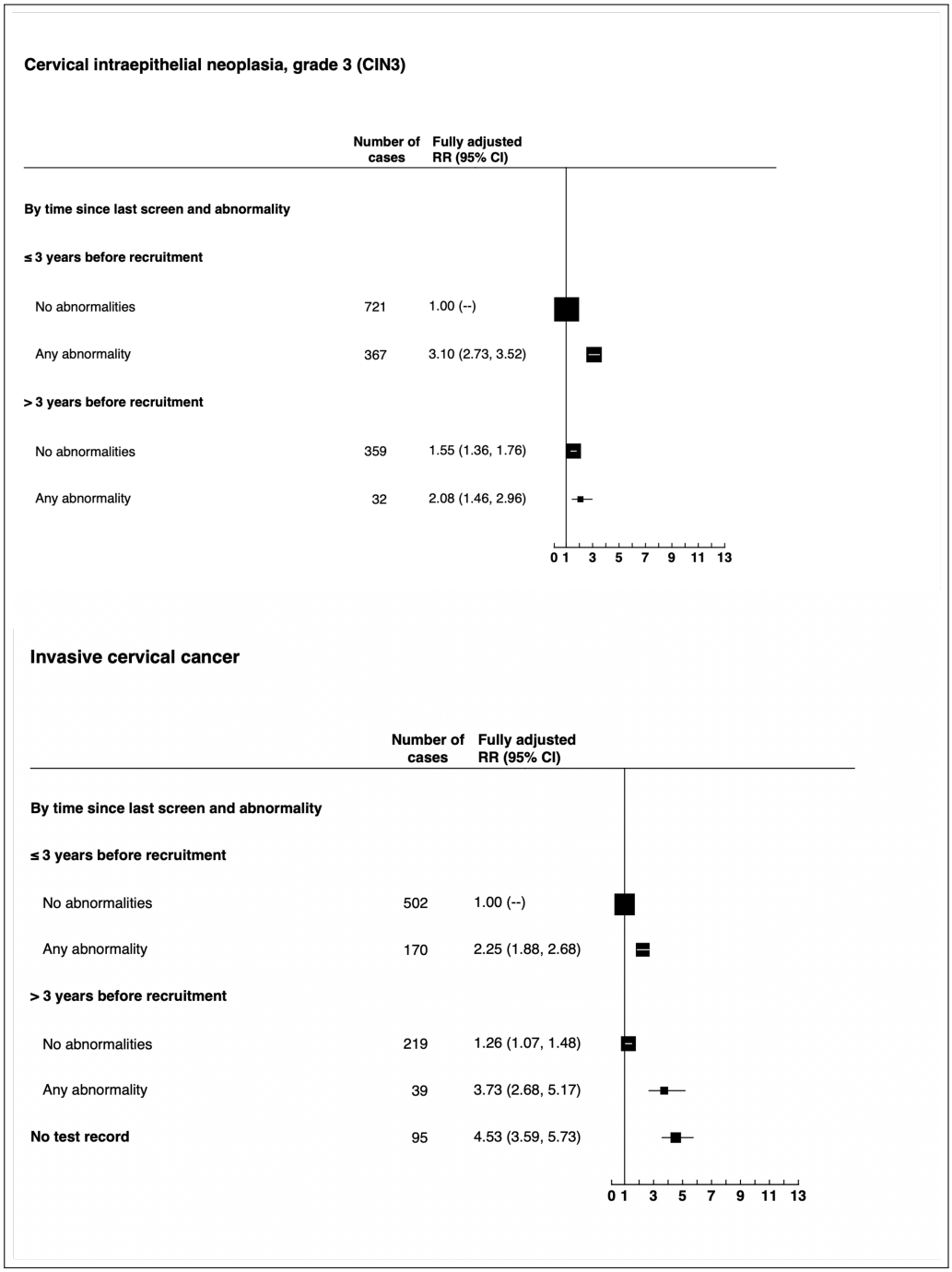
Table C.1: Recruitment characteristics of women included in analyses of risk of cervical intraepithelial neoplasia, grade 3 (CIN3) analyses in relation to screening history defined as time since last test and previous abnormality

* unless otherwise indicated

Estimates calculated in women with no missing values

C.1.1.1 Sensitivity analyses

Figure C.1: Minimally and fully adjusted relative risks (RR) and 95% confidence intervals (CI) of A: Invasive cervical cancer and B: Cervical intraepithelial neoplasia grade 3 (CIN3) in relation to past screening history (time since last test $\leq 3/>3$ years before recruitment)



D

Reproductive factors and the risk of cervical neoplasia

D.1 Results

D.1.1 Study participants

	% (n) of women*	
	Parous	**Nulliparous**
Mean age at baseline (SD)	56.1 (4.4)	55.9 (4.5)
Most deprived tertile	33 (245 595)	31 (27 053)
No educational qualifications	44 (324 582)	34 (28 604)
Body mass index 30+kg/m^2	17 (121 232)	15 (12 680)
Current smokers	19 (144 373)	17 (14 814)
Ever oral contraceptive use	62 (465 156)	51 (44 262)
Ever menopausal hormone therapy use	45 (332 357)	44 (37 822)

Table D.1: Recruitment characteristics of women included in analyses of risk of cervical intraepithelial neoplasia, grade 3 (CIN3) according to according to parity

* unless otherwise indicated

Estimates calculated in women with no missing values

	% (n) of women*		
	Nulliparous	**Parous, 1 FTP**	**Parous, 2+ FTP**
Mean age at baseline (SD)	56.1 (4.5)	56.0 (4.5)	56.2 (4.4)
Most deprived tertile	32(31 724)	32 (36 422)	33 (217 190)
No educational qualifications	34 (33 037)	44 (48 379)	45 (285 420)
Body mass index 30+ kg/m^2	16 (14 969)	16 (17 342)	17 (107 708)
Current smokers	17(16 501)	21 (23 211)	19 (126 831)
Ever oral contraceptive use	47 (46 366)	60 (66 803)	63 (408 906)
Ever menopausal hormone therapy use	41 (40 089)	44 (49 677)	44 (287 959)
No screening test record	12 (11 488)	2 (2431)	2 (10 205)

Table D.2: Recruitment characteristics of women included in analyses of risk of invasive cervical cancer according to number of full-term pregnancies (FTP)

* unless otherwise indicated

Estimates calculated in women with no missing values

	% (n) of women*	
	Less than 25 years at first FTP	**25+ years at first FTP**
Mean age at baseline (SD)	56.1 (4.3)	56.1 (4.5)
Most deprived tertile	38 (169 382)	25 (75 630)
No educational qualifications	54 (231 162)	30 (91 209)
Body mass index 30+ kg/m^2	19 (78 571)	15 (42 941)
Current smokers	23 (102 627)	14 (42 293)
Ever oral contraceptive use	63 (275 834)	62 (188 908)
Ever menopausal hormone therapy use	46 (201 475)	42 (127 481)
No screening test record	2 (7220)	2 (4968)

Table D.3: Recruitment characteristics of women included in analyses of risk of invasive cervical cancer according to age at first full-term pregnancy (FTP)

* unless otherwise indicated

Estimates calculated in women with no missing values

E

Oral contraceptives and the risk of cervical neoplasia

E.1 Results

E.1.1 Study participants

	% (n) of women*	
	Never users	**Ever users**
Mean age at baseline (SD)	57.7 (4.3)	55.1 (4.1)
Most deprived tertile	34 (109 785)	31 (160 537)
No educational qualifications	51 (159 338)	38 (190 589)
Body mass index 30+ kg/m^2	19 (57 090)	16 (75 910)
Current smokers	17 (53 976)	20 (104 025)
Ever menopausal hormone therapy use	36 (116 701)	50 (251 702)
Nulliparous	13 (42 036)	9 (44 262)
Age at first birth $<$ 18 years (parous)	2 (5 949)	3 (13 804)

Table E.1: Characteristics of women at recruitment in relation to never versus ever use of oral contraceptives

* unless otherwise indicated
Estimates calculated in women with no missing values

F

Menopausal hormone therapy and the risk of cervical neoplasia

F.1 Methods

F.1.1 Statistical analysis

Questionnaires answered	Rules for updating MHT use
Recruitment only	Set never, past or current use to unknown four years after recruitment
Recruitment; 2001 resurvey	• Set never, past or current use to unknown four years after recruitment and update use at 2001 resurvey • Set current use to unknown four years after 2001 resurvey • Never/past users at 2001 resurvey remain in their respective categories until the end of follow-up
Recruitment; 2006 resurvey	• Set never, past or current use to unknown four years after recruitment and update use at 2006 resurvey • Set current use to unknown four years after 2006 resurvey • Never/past users at 2006 resurvey remain in their respective categories until the end of follow-up
Recruitment; 2001 resurvey; 2006 resurvey	• Set never, past or current use to unknown four years after recruitment and update use at 2001 resurvey • Set never, past or current use to unknown four years after 2001 resurvey and update use at 2006 resurvey • Set current use to unknown four years after 2006 resurvey • Never/past users at 2006 resurvey remain in their respective categories until the end of follow-up

Table F.1: Rules for varying MHT use over time developed for the Million Women Study

F.2 Results

F.2.1 Study Participants- CIN3

Characteristics at baseline	% (n) of women* Never users	Ever users
Mean age at baseline (SD)	56.3 (4.7)	55.9 (4.1)
Most deprived tertile	32 (152 320)	31 (117 645)
No educational qualifications	45 (201 239)	40 (148 299)
Body mass index 30+ kg/m^2	18 (80 322)	15 (52 475)
Current smokers	18 (80 493)	21 (77 317)
Nulliparous	11 (48 564)	10 (37 822)
Age at first birth <18 years, parous	2.2 (9690)	2.1 (10 021)
Ever oral contraceptive use	55 (254 570)	68 (251 702)

Table F.2: Characteristics of women at study baseline in relation to never versus ever use of menopausal hormone therapy

* unless otherwise indicated

Our histories cling to us. We are shaped by where we come from.

— Chimamanda Ngozi Adichie

G

Study protocol: Evaluation of the data quality of reproductive cancers in the Nairobi Cancer Registry

G.1 Introduction

Non-communicable diseases, particularly cancers, are an emerging health problem in Sub-Saharan Africa (SSA). In Kenya, it is estimated that a total of 42,116 incident cancers occurred in 2020.[1] Of these, 60% of cases were estimated to have occurred in women.[311] Breast cancer was the most common cancer with an estimated age-standardised incidence rate (ASIR) of 41 per 100,000 and cervical cancer was the third most common cause of cancer in women with an ASIR of 31.3 per 100,000.[1] However, nationwide data are not available and estimates of cancer incidence and mortality are based on data from population-based cancer registries (PBCR) covering sub-national populations.

The Nairobi Cancer Registry (NCR), based in the capital city of Kenya, was established in the year 2001 and is one of 2 PBCRs in Kenya.[312] Since its establishment the NCR has attempted to register all incident cancer cases in usual Nairobi residents. In a recent report from the NCR, it was similarly estimated that breast cancer was the most common cancer among females in Nairobi accounting

for 23% of all cases, with an ASIR of 51.7 per 100,000. Cervical cancer ranked second (21.1% of cancers, age-standardised incidence 46.1 per 100,000). These two cancers comprised 44% of all female cancers. [312]

The NCR is therefore important in providing information on the incidence of cancers in Nairobi, and broadly Kenya, allowing insight into the burden of cancer in women in SSA, but the quality of the data has never been formally assessed. This study will be the first comprehensive analysis of the data quality of gynaecologic cancer registrations including breast, cervical, ovarian and endometrial cancers, at the NCR during the period 2007-2017. [310]

G.2 Aims and Objectives

The principal aim of this research is to reliably assess the data quality in the NCR from three different aspects: validity, comparability and completeness using the methods described by Bray and Parkin[310].

G.3 Methods

G.3.1 Data sources

G.3.1.1 The Nairobi Cancer Registry

Data on incident cancers from 2007-2017 will be extracted from the NCR CanReg 5.0 database.[313]

The NCR was established in 2001 in partnership with the Ministry of Health (MOH) and Kenya Medical Research Institute (KEMRI) and reports data on all residents of Nairobi. A resident is defined as a person who has continuously lived/worked in Nairobi for a period of at least six months and excludes those referred to the city for purposes of accessing treatment.[312]

Registry procedures have been described in detail previously.[312, 314] Briefly, the registry collects data from governmental and private hospitals and diagnostic laboratories; radiotherapy treatment centres; the Nairobi Hospice; and vital statistics registrations i.e. death certificates mentioning cancer. Active case-finding is employed at the registry and trained NCR registrars are regularly deployed to various hospitals to identify and abstract case information. Relevant information on cases is abstracted onto standard registration forms (**see Figure G.1**).

Variables collected include: patient details (name, ID number, age/date of birth, gender, concurrent illness, current residence, place of birth, religion and tribe/ethnicity); tumour details (incidence date, basis of diagnosis, primary site, histology/morphology, behaviour, grade and stage at diagnosis); treatment (initial and subsequent treatments- surgery, radiotherapy, chemotherapy, hormone therapy or palliative); sources of data and follow-up (patient status alive or dead). Death certificates mentioning cancer are also identified from the Department of Civil

Registration [315], and information abstracted for Nairobi residents. These cases are matched against the registry database, and for cases already registered, status at last contact is updated. Trace-back procedures are attempted for unmatched forms to verify cancer diagnoses using clinical records. Unmatched cases are registered as "death-certificate only" (DCO).

Coding of tumour site and histology is done according to International Classification of Diseases for Oncology (ICD-O-3)[316] CanReg5[313] automatically converts the pairs of topography/morphology codes to the appropriate code in the 10th revision of the International Classification of Diseases (ICD-10). Multiple primary cancers are defined according to the 2004 IARC rules.[317] Similarly, the registry adheres to IARC guidelines on confidentiality in connection with or during the collection, storage, use, and transmission of identifiable data.

G.3.1.2 Population data

Population at risk will be derived from national demographic censuses (Kenya Population and Housing Census [318]) conducted in 2009 and 2019 which provide the number of residents of Nairobi by age group and sex. Based on the reported annual population growth rate estimate in each sex and five-year age group, intercensal population sizes will be estimated for the years 2007-2017.

G.3.1.3 Outcome definition

Primary sites of female cancers to be examined were determined by frequency of occurrence in Nairobi and will include: invasive breast (ICD-C50), cervix uteri (ICD-C53), ovary (ICD-C56), endometrium (ICD-C54) and a composite group of "other gynaecologic cancers" including vulval (ICD-C51)and vaginal (ICD-C52) cancers

G.3.2 Registry data evaluation

G.3.2.1 Comparability

Comparability, defined as the extent to which classification and coding of new cases and basic definitions of incidence are consistent with agreed international guidelines,[310] will be assessed in the following aspects:

1. The system used for classification and coding of neoplasms as per World Health Organisations (WHO) International Classification of Disease (ICD) rules. [316]

2. The definition of incidence i.e what is defined as a new case as per European network of cancer registries (ENCR) rules.[319]

3. Distinguishing between a new case i.e., a primary cancer, and an extension, recurrence or metastasis of an existing one as per International Agency for Research on Cancer (IARC) rules [317]

G.3.2.2 Validity

Validity is defined as "the proportion of cases in a data-set with a given characteristic (e.g site and age) which truly have the attribute". The validity of the will be primarily assessed using the re-abstraction method introduced by Bray and Parkin.[310] Preliminary analyses of registration validity will be conducted by comparing diagnostic criteria i.e., histological verification and death certificate only registration cases with neighbouring registries.

Re-abstraction

Validity will be assessed by re-abstraction of data from medical records from patients reported to the register during four separate years (2007, 2010, 2013 and 2016) to assess if any changes in abstraction forms/guidelines over the years have affected validity. For each year, 10% of all reported patients will be randomly selected for validation. Medical records will be retrieved and data re-abstraction will be performed according to NCR abstraction guidelines for cancer registry records.

Re-abstraction will be performed by a new team of trained staff with no affiliation to the NCR. Variables will include date of birth, county and current residence, date of diagnosis, basis of diagnosis, primary site two-digit topology code, malignant behaviour, stage, grade, five-digit morphology code, life status, and last contact date, which will be retrieved from registered data and reviewed.

Statistical analysis for validity will be performed by calculating the exact agreement between original data recorded in the NCR and re-abstracted data. The exact agreement refers to the proportion of posts where the reported information is identical to the re-abstracted information. The strength of agreement will be measured by Cohen's κ for categorical variables, Kendall's τ for ordinal categorical variables and Pearson correlation for numerical variables. The strength of agreement according to the Cohen's kappa will be interpreted according to the following scale; poor (<0.00), slight(0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) and almost perfect (0.81–1.00).[320]

G.3.2.3 Completeness

Completeness is defined as "the extent to which all of the incident cancers occurring in the population are included in the registry database."[310] Two methods will be used as described by Parkin and Bray; semi-quantitative and quantitative.

Semi-quantitative methods

Three semi-quantitative methods will be used to ascertain completeness. First, comparison will be made of the annual age-specific incidence rates in the period 2007- 2017 and annual age standardised rates (using the world standard population) to estimate the stability of incidence over time, looking for abnormal trends or patterns. Second, the age-standardised incidence rates of female neoplasms in the NCR will also then be compared to other African cancer registries with the assumption that the incidence rates for these cancers will be similar in the SSA region. Age-specific incidence curves will be drawn for each site of cancer looking for abnormal patterns. Finally, the average number of notifications per case for the period of 2007-2017 will be obtained.

Quantitative methods

One of the main quantitative methods is independent case ascertainment as reproduced to evaluate the Kampala Cancer Registry.[321] Independent case ascertainment involves comparison of the registry database with sets of cancer cases that have been compiled independently of the cancer registry's case-finding procedures. This method will be used to ascertain completeness of breast cancer registrations using cases identified in a Kenyan breast cancer cohort. This study has been described in detail previously.[322] Briefly, this study recruited patients with pathologically confirmed breast cancer (n=510) between March 2012 and May 2015 registered at collaborating hospitals in Kenya including 3 in Nairobi. Record linkage of the cancer registry database and this independent case series will be used to estimate the number of cases registered in Nairobi in the latter "missed' by the registry. The proportion of patients already registered is a direct quantitative estimate of completeness.

G.4 Consent, confidentiality and ethics

The study protocol will be submitted for approval by the KEMRI Scientific Steering Committee and Ethics Review Committee. This study will use anonymised and encrypted data from the NCR database.

G.5 Publication of results

Any results from this study will be published in peer-reviewed journals and where appropriate the relevant authorities (e.g. the Ministry of Health) will be notified of the findings.

Figure G.1: Nairobi Cancer Registry, Standard Abstract Form

APPENDIX D - ABSTRACT FORM

CONFIDENTIAL

NAIROBI CANCER REGISTRY:

CANCER ABSTRACT FORM:

REGISTRY NUMBER ☐☐☐☐☐☐☐☐

A. PATIENT: NAMES	1. FIRST	2. GIVEN	3. FAMILY

4. National Identification No. _____

5. Age ☐☐ 6. Date of Birth d d ☐☐ m m ☐☐ y y y y ☐☐☐☐ 7.Sex___(1=Male 2=Female 9=Unk)

8. Concurrent Illness_____

9. Place of Residence_____ ☐☐☐

10.Place of Birth_____ ☐☐☐ 11. Tribe_____ ☐☐

12. Religion ☐ 1 – Christian 2 – Muslim 3 – Hindu 4 – Other

B. TUMOUR:

13. Incidence date d d ☐☐ m m ☐☐ y y y y ☐☐☐☐

14. Basis of Diagnosis ☐
0 – Death cert only
1 – Clinical only
2 – Clinic. Invest./ Ultra sound
4 – Biochem. Immuno test
5 – Cytology/Haematology
6 – Histology of metastasis
7 – Histology of primary
9 – Unknown

15. Primary Site _____C._____

16. Histology _____ M ☐☐☐☐

17. Behaviour ☐
0 – Benign
1 – Uncertain
2 – In situ
3 – Malignant

18. Grade ☐
1 – Well diff 6 – B-Cell
2 – Moderately diff
7 – Null Cell
3 – Poorly diff. 8 – Killer cell
4 – Undifferentiated/Anaplastic
5 – T-cell
9 – Unknown

19. Stage ☐
0 – InSitu
1 – Stage I
2 – Stage II
3 – Stage III
4 – Stage IV
9 – Unknown

T_____
N_____
M_____

C. TREATMENT: (1=NO; 2=YES; 9=UNKNOWN)

20.Surgery ☐ Radiotherapy ☐ Chemotherapy ☐ Hormone Therapy ☐ Symptomatic ☐

D. SOURCES:

21. Source 1. Hosp._____Hosp. No. _____ SRC date 1_____

22. Source 2. Lab._____ Lab. No. _____ SRC date 2_____

E. FOLLOW UP:

23. Present Status 1=Alive 2= Dead ☐ 24. Date Last Contact/Date of death: _____ / _____/ _____

25. Hospice No. _____If Dead Cause of Death_____

Remarks if any:_____

Form filled by_____ Date_____

Cancer Incidence Report Nairobi 2000 - 2002

Figure G.2: Murray Speight Grant Award Letter

RHODES TRUST

Amber Reast
Assistant Registrar, Scholar Affairs
scholar.affairs@rhodeshouse.ox.ac.uk

10 June 2021

Dear Karima,

I am pleased to inform you that your application for the Murray Speight Research Grant 2021 has been successful. The amount awarded to you is £1060 to be used to access the Nairobi and Eldoret cancer registries. Please note the funds you have been awarded must be spent in this calendar year (ie. by 31st December 2021).

As you know, resources are limited and each year this remains a competitive process. Therefore, we would ask that if you receive funding from alternative sources in excess of the amount for which you initially applied, that you claim from us only the funds that you require. Any unclaimed amounts will remain in the overall fund available to support the research of future Scholars who apply.

If you need an advance of funds against the expenditure itemised in your application, please apply to Paul Smith (scholar.finances@rhodeshouse.ox.ac.uk), who will require receipts against all budgeted expenditure at the conclusion of your project. Alternatively, you can submit a request to Paul for a refund of your expenditure, against receipt, after it has been incurred. In both instances, requests must be received by 31st December 2021.

Please note that this award has been made for the project specified in your application. If you are considering altering your plans in any material way, please contact me first.

Kindly note that all recipients are expected to submit a post-activity report within one month of their return/completion of the project and no later than 31 December 2021.

Many congratulations and I wish you all the best with your research.

Yours sincerely,

Amber Reast

Amber Reast
Assistant Registrar