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Clinical Research Article

Reproductive Factors in Relation to Incidence of Lung and Colorectal Cancers in a Cohort of Norwegian Women: The HUNT Study

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Abstract

Context: The roles of reproductive factors in the etiology of lung and colorectal cancers, among the most common cancers in women, are unclear.

Objective: We aimed to explore whether female reproductive factors were associated with the incidence of lung and colorectal cancers.

Methods: We followed up 33 314 cancer-free women who participated in the HUNT Study in Norway from 1995-1997 to 2018. A large panel of reproductive factors were self-reported at baseline. Incident lung and colorectal cancer cases were ascertained from the Cancer Registry of Norway. Cox regression models were used to estimate hazard ratios (HRs) with 95% CIs after adjustment for important confounders.

Results: During a median follow-up interval of 22.2 years, 467 women developed lung cancer (including 169 lung adenocarcinoma), 660 developed colon cancer, and 211 had rectal cancer. Early menarche (≤12 years) was associated with an increased incidence of lung adenocarcinoma (HR 1.43; 95% CI, 1.02-2.03). Women with one or no child had an increased colon cancer incidence (HR 1.26; 95% CI, 1.03-1.54). Hormone therapy appeared to be associated with a decreased incidence of rectal cancer (HR 0.68; 95% CI, 0.44-1.04). Results in the subgroup of postmenopausal women were similar or strengthened. Other reproductive factors were not related to the risk of lung, colon, and rectal cancers.

Conclusion: Certain reproductive factors might play a role in the etiology of lung and colorectal cancers. Further investigations are warranted to study if they are causal associations.

Key Words: colorectal cancer, HUNT, lung cancer, menarche, prospective cohort, reproductive factors

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ER, estrogen receptor; HUNT, Trøndelag Health Study; MR, Mendelian randomization; REK, Regional Committees for Medical and Health Research Ethics.

Breast cancer is the most common cancer in women [1]. Reproductive factors such as early menarche, late age at first live birth, and a low number of children have been identified as risk factors for developing breast cancer [2]. Lung and colorectal cancers are the second and third leading cause of cancer death in women worldwide [1]. Their incidence rates in women are approximately 4-fold higher in transitioned countries than in transitioning countries, and the incidence rate of colon cancer is the highest in Norway [1]. In many countries, lung cancer morbidity and mortality have been decreasing among men but increasing among women [1]. Although a large part can be explained by changes in smoking habits, factors that are specific for women may have played a role [3], and besides, around 20% of European female individuals with lung cancer have never smoked [4]. There are 2 broad histologic classes of lung cancer: small cell lung cancer and non-small cell lung cancer, including adenocarcinoma [5]. Tobacco smoking is strongly associated with small cell lung cancer but less strongly with lung adenocarcinoma [5, 6]. Unlike lung cancer, no single risk factor accounts for most of the cases of colorectal

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cancer. The incidence rates of colorectal cancer are increasing in young adults [7, 8].

Although lung and colorectal cancers are among the most common cancers in women [1], the roles of reproductive factors in the etiology of these 2 cancers are less clear. Several studies have suggested that female sex hormones and reproductive factors may play a role in lung and colorectal tumorigenesis [9–17]. Estrogen receptors α and β (ERα and ERβ) are expressed in both normal and cancerous lung and colonic cells [17–19]. Reproductive factors, such as age at menarche, at menopause, or at first birth, as well as number of children, have been used as surrogate markers for lifetime exposure to endogenous estrogens. They have been identified as risk factors for sex hormone–related malignancies such as breast cancer [2]. However, results from epidemiological studies investigating the relationships between these reproductive factors and risks of lung cancer and colorectal cancer are inconsistent [20–23].

In Norway, the fertility rate has decreased and the maternal age at first birth has increased over the last decades [24]. Thus, we aimed to investigate if female reproductive factors were associated with the incidence of lung cancer overall and its histologic types as well as with the incidences of colon and rectal cancers. We hypothesized that reproductive factors reflecting a lifetime exposure to higher levels of endogenous estrogen were associated with an increased incidence of lung and colorectal cancers.

Materials and Methods

Study Design and Population

The Trøndelag Health Study (HUNT) is one of the largest collections of health data in Norway [25]. The study enrolled participants aged 18 years or older in 4 surveys: HUNT1 (1984-1986), HUNT2 (1995-1997), HUNT3 (2006-2008), and HUNT4 (2017-2019). All adults living in the area of northern Trøndelag, Norway were invited to complete general questionnaires on health and lifestyle factors, and to undergo clinical examinations [25, 26].

For the current study we included a total of 34 656 women from the HUNT2 survey (the response rate was 70%). Each participant was followed from the date of participation in HUNT2 until the date of first diagnosis of lung or colorectal cancer, the date of death or emigration from Norway, or the end of the follow-up period on December 31, 2018, whichever came first. Diagnoses of lung and colorectal cancers were obtained from the Cancer Registry of Norway. Information on vital status and emigration was obtained from the National Population Registry. Among the 34 656 women, we excluded 1342 female participants with previous cancer diagnoses before baseline, based on information from the Cancer Registry of Norway, leaving 33 314 participants in the study population.

The study has been approved by the Regional Committees for Medical and Health Research Ethics (REK South-East 2019/337). All participants signed informed written consent on participation in HUNT, with linkage to previous HUNT surveys and specific registries in accordance with the Declaration of Helsinki.

Measurement of Exposures

Female reproductive factors were collected in the HUNT2 questionnaires, including age at menarche and at menopause, surgery of ovaries or uterus, number of children, age at first birth, oral contraceptive use and duration, and hormone therapy. Premenopausal women were defined as those who reported still having menstruation and did not report age at menopause or a history of bilateral oophorectomy or hysterectomy. Women who had missing information on menstruation status were also defined as premenopausal if they were younger than 48 years (mean age at menopause of the study population) and did not report a history of bilateral oophorectomy or hysterectomy. Postmenopausal women were defined as those who reported an age at menopause or a history of bilateral oophorectomy or hysterectomy. Menopause was considered as non-natural if both ovaries and/or uterus were surgically removed before or at the age of menopause, or if women only reported age at one of these surgeries but not at menopause. The remaining menopausal women were defined as natural menopause except those who did not report age at the 2 surgeries and at menopause. Reproductive period was calculated by subtracting age at menarche from age at menopause. Hormone therapy users were defined as women reporting current or previous use of systemic estrogen medicines (tablets or patches), while nonusers as women reporting "never use" of estrogen. Among ever-users, 26% were premenopausal and 71% were postmenopausal women.

We explored the following 8 reproductive factors as the main exposures: age at menarche, age at menopause, menopause status (natural/non-natural), reproductive period, number of children, age at first birth, and oral contraceptive and hormone therapy. Cutoff points for exposures were set at population means ± 1 SD. We assumed that early menarche, late menopause, and long reproductive period reflected exposure to higher levels of endogenous estrogen, and that women with low number of children or late age at first birth might have an increased risk of developing lung or colorectal cancers. Thus, early menarche and low number of children were defined using the cutoff points at population mean − 1 SD. More specifically, early menarche was defined as menarche at the age of 12 years or before (≤ 12 vs > 12 years as the reference group), and low number of children specified as having 1 or no child (0-1 vs > 1 as the reference group). The cutoff for late age at menopause, long reproductive period, and late age at first birth were defined using population mean + 1 SD. More specifically, menopause was considered late after age of 54 years (≥ 54 vs < 54 years as the reference group), long reproductive period was after 40 years (≥ 40 vs < 40 years as the reference group), and late age at first birth after age of 28 years (≥ 28 vs < 28 years as the reference group).

Other Baseline Variables

Weight and height were measured by health professionals at clinical examination. Body mass index (BMI) was calculated as weight divided by the squared value of height (kg/m²) and was grouped into 4 categories (<18.5, 18.5-24.9, 25.0-29.9, and ≥30.0 kg/m²) according to the recommendations of the World Health Organization [27]. Based on information of smoking status and pack-years, participants were classified into the detailed categories of smoking: never, former (≤10, 10.1-20, >20 pack-years) and current (≤10, 10.1-20, >20 pack-years). Other covariates were categorized as: passive smoking (never, ever), alcohol consumption (never, 1-4, ≥5 times/month), physical activity (inactive, low, moderate, high), total sitting time daily (0-4, 5-7, ≥8 hours), education

(<10, 10-12, ≥13 years), economic difficulties (yes, no) based on a question "During the last year, has it at any time been difficult to meet the costs of food, transportation, housing and such?" to represent social status, family history of cancer (yes, no) based on "Is there any family member such as father, mother, siblings, children who reported cancer?", reported doctor-diagnosed chronic obstructive pulmonary disease (COPD) (yes, no) based on "Have you been diagnosed as having chronic bronchitis or emphysema by a doctor?", and history of diabetes (yes, no) was based on the question: "Have you had, or do you have diabetes?" and/or non-fasting blood glucose level ≥11 mmol/L. Missing information on each covariate was classified as an "unknown" category and included in the analyses. The categorization of covariates in the current study were commonly used in previous HUNT publications [28, 29].

Ascertainment of Lung and Colorectal Cancers

Participants' information from HUNT2 was linked to the Cancer Registry of Norway using the 11-digit personal identification number. Data from the Cancer Registry of Norway are considered reasonably accurate, close-to-complete and timely [30]. The Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems codes used for registration of lung cancer, colon cancer, and rectal cancer were C33-C34, C18, and C19-C20, respectively. Lung cancer histologic types were classified according to the International Classification of Disease of Oncology [31]. They were further categorized into adenocarcinoma and non-adenocarcinoma including all other cell types in the current study based on possible difference in etiology [4] and the same classification in previous studies [32, 33] to increase statistical power.

Statistical Analysis

As different reproductive factors might be associated with the cancer incidence in pre- or postmenopausal women [16], statistical analyses were performed in all women and in postmenopausal women as a subset. Analyses were not performed in premenopausal women due to small number of cancer cases. Characteristics of the participants were presented. Cox proportional hazard models were used to explore the potential associations of reproductive factors with lung cancer overall and its subtypes as well as with colon cancer, rectal cancer, and colorectal cancer. Crude and adjusted hazard ratios (HRs) with 95% CIs were calculated with age as the timescale. In the adjusted model, detailed categories of smoking status combined with pack-years was used to minimize confounding by smoking. The model was also adjusted for potential confounders, such as BMI, passive smoking, alcohol consumption, physical activity, total sitting time daily, education, social status, family history of cancer, reported COPD (only for lung cancer), and history of diabetes (only for colon cancer, rectal cancer, and colorectal cancer).

We assessed the proportional hazards assumption by Schoenfeld residuals for exposures and all covariates. We used the *tvc* option of the *stcox* command in Stata to model the nonproportional hazards for covariates such as smoking, passive smoking, and social status. We used the bootstrapping method when an exposure variable did not meet the proportional hazards assumption [34], which applied to the analysis about number of children in relation to colon cancer and age at menarche in relation to rectal cancer in all women. We added the *vce(boot)* option to the *stcox* command.

We performed several sensitivity analyses to test the robustness of our findings: (1) Multiple imputation with chained equations (m = 20 imputed datasets) was used to address residual confounding due to missing data of the covariates, based on the assumption of missing at random [35]. (2) As suggested by VanderWeele et al, we computed E-values in order to assess the influence of unmeasured confounding [36]. A large E-value implies that a large unmeasured confounding would be needed to fully explain away a specific exposure-outcome association. (3) To address a potential reverse causation by existing but undiagnosed rectal cancer in relation to the use of hormone therapy, we excluded the first 3-year follow-up.

All statistical analyses were performed with STATA/MP 17 (College Station, TX, USA).

Results

In total, 467 women developed lung cancer during a median follow-up period of 22.2 years, and among them, 169 had lung adenocarcinoma. During the same follow-up period, 660 and 211 women developed colon cancer and rectal cancer, respectively. Table 1 describes the characteristics for all women and Supplementary Table S1 for postmenopausal

Table 1. Characteristics in all women (*n* = 33 314) in HUNT2, 1995-1997

Variables	All women
Number of subjects	33 314
Age (years)	49.6 ± 17.4
Body mass index (kg/m^2)	26.2 ± 4.6
Number of lung cancer cases (%)	467 (1.4)
Number of colorectal cancer cases (%) Colon cases (%) Rectal cases (%)	871 (2.6) 660 (2.0) 211 (0.6)
Smoking status, % (never/former/current/unknown)	47.2/21.2/29.1/2.5
Passive smoking, % (never/ever/unknown)	17.3/80.9/1.8
Alcohol consumption (times/month), % (never/1-4/≥5/unknown)	43.1/40.7/6.8/9.4
Physical activity, % (inactive[a]/active[b]/unknown)	23.4/42.1/34.5
Total sitting time daily (hours), % (0-4/5-7/≥8/unknown)	25.7/25.0/25.1/24.2
Education (years), % (<10/10-12/≥13/unknown)	37.5/27.3/29.6/5.6
Economic difficulties, % (no/yes/unknown)	48.1/22.8/29.2
Family history of cancer, % (no/yes)	72.7/27.3
Reported chronic obstructive pulmonary disease (COPD), % (no/yes)	98.0/2.0
History of diabetes, % (no/yes/unknown)	96.8/3.0/0.2

Data are given as mean ± SD for continuous variables.
[a]Inactive: women with no physical activity or ≤ 2 hours light activity only per week.
[b]Active: women with low, moderate, or high level of physical activity. Physical activity level classified as low (≥ 3 hours light activity only per week, or ≤ 2 hours light activity and < 1 hour hard activity per week), moderate (≥ 3 hours light activity and < 1 hour hard activity per week, or 1-2 hours hard activity per week regardless of light activity) or high (≥ 3 hours hard activity per week regardless of light activity).

women only [37]. The mean age of all participants was 49.6 years, with 50.3% being ever smokers and 80.9% being ever passive smokers. The distribution patterns for most of the characteristics were similar between all women and postmenopausal women, except that postmenopausal women had a higher BMI and higher percentages of family history of cancer, low education, and never smokers compared with all women.

Early menarche was not associated with the incidence of lung cancer overall in all women (HR 1.10; 95% CI, 0.88-1.38), but it was associated with an increased incidence of lung adenocarcinoma (HR 1.43; 95% CI, 1.02-2.03) (Table 2). Similar results for lung adenocarcinoma were observed among postmenopausal women ($n = 12\,210$), and the corresponding HR for lung adenocarcinoma was 1.46 (95% CI, 0.89-2.39) with a wider 95% CI (Supplementary Table S2) [37]. The association held when using age at menarche as a continuous variable. One year earlier in age at menarche was associated with a HR of 1.12 (95% CI, 1.01-1.27) for lung adenocarcinoma in all women. There was no clear association of early menarche with the incidence of lung non-adenocarcinoma in all women or postmenopausal women (HR 0.94; 95% CI, 0.70-1.25 and HR 1.22; 95% CI, 0.85-1.74, respectively) (Supplementary Table S3) [37]. The distribution of ever smokers was similar among women with early menarche compared to those with late menarche in all women as well as in postmenopausal women (54% vs 50% and 49% vs 45%, respectively).

Concerning reproductive factors and colorectal cancer incidence, women with 1 or no child had an increased colon cancer incidence (HR 1.26; 95% CI, 1.03-1.54) (Table 3), and the HR was 1.44 (95% CI, 1.14-1.82) among the postmenopausal women (Supplementary Table S4) [37]. The associations were persistent using number of children as a continuous variable. Having one less child was associated with a HR of 1.05 (95% CI, 1.00-1.11) for colon cancer in all women. Having 1 or no child was also associated with an increased risk of colorectal cancer overall (HR 1.17; 95% CI, 0.98-1.39), particularly among postmenopausal women (HR 1.28; 95% CI, 1.03-1.59) (Supplementary Table S5) [37]. Hormone therapy, on the other hand, appeared to be associated with a decreased incidence of rectal cancer in all women (HR 0.68; 95% CI, 0.44-1.04) (Table 3) and this inverse association was stronger in postmenopausal women (HR 0.40; 95% CI, 0.22-0.73) (Supplementary Table S4) [37]. Hormone therapy was not associated with colorectal cancer overall incidence (Supplementary Table S5) [37]. Other reproductive factors, such as age at menopause, menopause status, reproductive period, age at first birth, and oral contraceptive use were not associated with the incidences of lung cancer and its subtypes, colon cancer, or rectal cancer in all women (Tables 2 and 3) or in postmenopausal women (Supplementary Tables S2–S5) [37]. Figure 1 illustrates our main findings.

Results from the following sensitivity analyses provided supportive evidence for our findings: (1) the analyses after performing multiple imputations for missing data of all covariates showed similar results (Supplementary Table S6) [37]; (2) the E-values were large for all the observed associations between age at menarche and lung adenocarcinoma, number of children and colon cancer, as well as hormone therapy and rectal cancer, specifically in the postmenopausal women (Supplementary Table S6) [37]; and (3) after excluding the first 3 years of follow-up, the results for the associations between hormone therapy and rectal cancer were similar (HR 0.73; 95% CI, 0.47-1.13 in all women and HR 0.42; 95% CI, 0.22-0.79 in postmenopausal women).

Discussion

Main Findings

In this prospective cohort study of all women participants, we found that early menarche was associated with an increased incidence of lung adenocarcinoma and that women with one or no child had an increased incidence of colon cancer. Moreover, hormone therapy was associated with a decreased incidence of rectal cancer. Results in the postmenopausal women showed similar or stronger associations.

Comparison With Previous Studies

The main results of the present study were to some extent consistent with results from previous reports. A meta-analysis including 24 studies by Zhang et al found that older age at menarche in North American women was associated with a significantly decreased risk of lung cancer [15]. Among studies included in this meta-analysis, a cohort study of 185 017 postmenopausal women showed that the significant inverse association was stronger for lung adenocarcinoma than for lung cancer overall [20]. This cohort study had some limitations such as a short follow-up of 6 to 10 years and no information on passive smoking for adjustment. In contrast, a recent systematic review and meta-analysis study reported that age at menarche was not associated with overall lung cancer or lung adenocarcinoma [14]. The modest association between early menarche and increased incidence of lung adenocarcinoma observed in our study needs to be interpreted cautiously as the estimate in postmenopausal women was imprecise.

A meta-analysis, including 21 923 colorectal adenomas cases, suggested that high number of children (having 4 or more children) and hormone therapy use might reduce the risk of colorectal adenomas [13]. One of the most recent prospective cohort studies of 93 676 postmenopausal women also found that having at least 2 children was associated with a lower colorectal cancer risk [23]. Another recent prospective cohort study of UK women, including 18 518 incident colorectal cancers, found that use of hormone therapy for the menopause was associated with a decreased risk of colorectal cancer, particularly rectal cancer [22]. Results from these 2 prospective cohort studies largely support our findings of the associations between number of children and colon cancer as well as between hormone therapy and rectal cancer. Overall, hormone therapy has been consistently linked with lower colorectal cancer risk both in observational studies and in randomized controlled trials [9–12]. Our findings replicated these results from randomized controlled trials. *The Lancet* report from 2014 mentioned the use of hormone therapy as a preventive measure for colorectal cancer [38]. However, it is important to note that the potential protective effect of hormone therapy in colon and rectal carcinogenesis may not counterbalance the harmful effect of hormone therapy on cardiovascular disease and breast cancer [39, 40]. Indeed, long-term use of hormone therapy, especially the combination of estrogen and progesterone, nearly doubled the risk of breast cancer [41]. Thus, the current recommendation is that women should use hormone therapy for symptomatic

Table 2. Reproductive factors in relation to incidence of lung cancer overall and lung adenocarcinoma in all women (n = 33 314) in HUNT2

			Lung cancer overall ($n = 467$)					Lung adenocarcinoma ($n = 169$)				
				Crude[a]		Adjusted[b]			Crude[a]		Adjusted[b]	
Reproductive factors		n[c]	Cases[c]	HR	95% CI	HR	95% CI	Cases[c]	HR	95% CI	HR	95% CI
Menstrual factors												
Age at menarche (yrs)	>12	24 375	351	1.00	Reference	1.00	Reference	120	1.00	Reference	1.00	Reference
	≤12	7820	104	1.15	0.92-1.43	1.10	0.88-1.38	46	1.41	1.00-1.99	1.43	1.02-2.03
Age at menopause (yrs)	Premenopausal & <54	28 440	353	1.00	Reference	1.00	Reference	134	1.00	Reference	1.00	Reference
	≥54	1413	30	0.86	0.59-1.26	1.15	0.78-1.68	10	0.85	0.44-1.63	1.14	0.59-2.21
Menopause status[d]	Premenopausal & Natural	28 285	349	1.00	Reference	1.00	Reference	130	1.00	Reference	1.00	Reference
	Nonnatural	1568	34	1.01	0.71-1.45	1.01	0.71-1.44	14	1.20	0.69-2.09	1.24	0.71-2.16
Reproductive period[e] (yrs)	Premenopausal & <40	27 786	343	1.00	Reference	1.00	Reference	135	1.00	Reference	1.00	Reference
	≥40	1678	37	0.88	0.62-1.24	1.12	0.79-1.59	9	0.60	0.30-1.19	0.77	0.39-1.52
Pregnancy factors												
Number of children	>1	24 460	395	1.00	Reference	1.00	Reference	139	1.00	Reference	1.00	Reference
	0-1	8581	71	0.97	0.75-1.25	0.92	0.71-1.19	30	1.16	0.78-1.73	1.09	0.73-1.63
Age at first birth (yrs)	Nulliparous & <28	28 701	425	1.00	Reference	1.00	Reference	152	1.00	Reference	1.00	Reference
	≥28	4167	41	0.59	0.43-0.82	0.87	0.62-1.20	17	0.73	0.44-1.21	0.98	0.59-1.64
Hormone use												
Oral contraceptive use (yrs)	Never	10 073	190	1.00	Reference	1.00	Reference	67	1.00	Reference	1.00	Reference
	Ever	13 260	116	1.33	1.03-1.72	1.20	0.93-1.55	48	1.31	0.87-1.98	1.11	0.73-1.69
	<4y of use	5238	49	1.28	0.92-1.78	1.19	0.85-1.66	21	1.32	0.78-2.22	1.15	0.67-1.95
	≥4y of use	7441	54	1.29	0.93-1.79	1.19	0.85-1.65	22	1.22	0.72-2.06	1.04	0.61-1.77
Hormone therapy[f]	Never	21 031	237	1.00	Reference	1.00	Reference	86	1.00	Reference	1.00	Reference
	Ever	3866	94	1.16	0.91-1.47	1.04	0.82-1.34	33	1.18	0.78-1.78	1.06	0.70-1.60

Abbreviation: CI, confidence interval; HR, hazard ratio.
[a]Age was used as the time scale in the crude model.
[b]Adjusted for body mass index, smoking, passive smoking, alcohol consumption, physical activity, sitting time, education, social status, family history of cancer, reported chronic obstructive pulmonary disease (COPD). Age was used as the time scale. *Tvc* option of the *stcox* command in Stata was used to model the non-proportional hazards for social status in the adjusted models.
[c]For each variable, the number does not meet the number of all women in HUNT2 ($n = 33\,314$) or all cancer cases because of missing data.
[d]Menopause status: defined as nonnatural if got bilateral oophorectomy and/or hysterectomy before or at age of menopause.
[e]Reproductive period: difference between age at menarche and age at menopause.
[f]Hormone therapy: includes systemic estrogen medicines (tablets, patches), except contraceptive pill.

Table 3. Reproductive factors in relation to incidence of colon cancer and rectal cancer in all women ($n = 33\,314$) in HUNT2

			Colon cancer ($n = 660$)					Rectal cancer ($n = 211$)				
				Crude[a]		Adjusted[b]			Crude[a]		Adjusted[b]	
Reproductive factors		n[d]	Cases[d]	HR	95% CI	HR	95% CI	Cases[d]	HR	95% CI	HR	95% CI
Menstrual factors												
Age at menarche (yrs)	>12	24 375	521	1.00	Reference	1.00	Reference	166	1.00	Reference	1.00	Reference
	≤12	7820	107	0.88	0.72-1.09	0.87	0.70-1.08	37	0.84	0.59-1.20	0.84[c]	0.59-1.19
Age at menopause (yrs)	Premenopausal & <54	28 440	496	1.00	Reference	1.00	Reference	170	1.00	Reference	1.00	Reference
	≥54	1413	57	0.97	0.74-1.28	0.96	0.73-1.27	11	0.70	0.38-1.30	0.73	0.39-1.36
Menopause status[e]	Premenopausal & Natural	28 285	502	1.00	Reference	1.00	Reference	169	1.00	Reference	1.00	Reference
	Nonnatural	1568	51	1.01	0.76-1.35	0.99	0.74-1.33	12	0.79	0.44-1.43	0.77	0.43-1.38
Reproductive period[f] (yrs)	Premenopausal & <40	27 786	465	1.00	Reference	1.00	Reference	162	1.00	Reference	1.00	Reference
	≥40	1678	72	1.11	0.86-1.42	1.09	0.84-1.40	16	0.87	0.51-1.47	0.90	0.53-1.53
Pregnancy factors												
Number of children	>1	24 460	522	1.00	Reference	1.00	Reference	179	1.00	Reference	1.00	Reference
	0-1	8581	131	1.25	1.03-1.52	1.26[c]	1.03-1.54	31	0.88	0.60-1.29	0.90	0.61-1.32
Age at first birth (yrs)	Nulliparous & <28	28 701	554	1.00	Reference	1.00	Reference	177	1.00	Reference	1.00	Reference
	≥28	4167	94	0.86	0.69-1.07	0.88	0.70-1.10	33	1.12	0.77-1.63	1.19	0.81-1.75
Hormone use												
Oral contraceptive use (yrs)	Never	10 073	266	1.00	Reference	1.00	Reference	82	1.00	Reference	1.00	Reference
	Ever	13 260	121	1.10	0.86-1.40	1.13	0.88-1.45	51	1.06	0.72-1.57	1.10	0.73-1.65
	<4y of use	5238	59	1.24	0.92-1.68	1.27	0.94-1.73	18	0.89	0.52-1.52	0.92	0.53-1.59
	≥4y of use	7441	52	0.97	0.70-1.34	1.01	0.72-1.40	30	1.27	0.80-2.02	1.33	0.82-2.14
Hormone therapy[g]	Never	21 031	336	1.00	Reference	1.00	Reference	125	1.00	Reference	1.00	Reference
	Ever	3866	114	1.07	0.87-1.33	1.07	0.86-1.33	27	0.67	0.44-1.03	0.68	0.44-1.04

Abbreviation: CI, confidence interval; HR, hazard ratio.
[a]Age was used as the time scale in the crude model.
[b]Adjusted for body mass index, smoking, passive smoking, alcohol consumption, physical activity, sitting time, education, social status, family history of cancer, history of diabetes. Age was used as the time scale. *Tvc* option of the *stcox* command in Stata was used to model the nonproportional hazards for passive smoking in the adjusted models.
[c]*Vce(boot)* option of the *stcox* command in Stata was used when an exposure variable did not meet the proportional hazards assumption in the adjusted models.
[d]For each variable, the number does not meet the number of all women in HUNT2 ($n = 33\,314$) or all cancer cases because of missing data.
[e]Menopause status: defined as nonnatural if got bilateral oophorectomy and/or hysterectomy before or at age of menopause.
[f]Reproductive period: difference between age at menarche and age at menopause.
[g]Hormone therapy: includes systemic estrogen medicines (tablets, patches), except contraceptive pills.

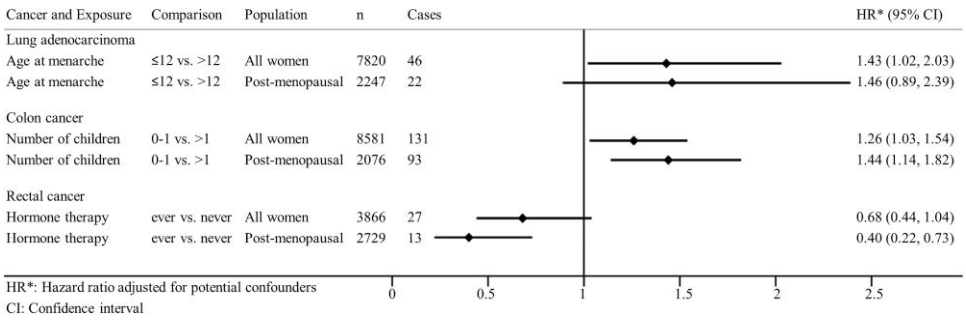

Figure 1. Illustration of our main findings between age at menarche and lung adenocarcinoma, number of children and colon cancer, as well as hormone therapy and rectal cancer in all women ($n = 33\,314$) and postmenopausal women ($n = 12\,210$) in HUNT2.

menopausal hot flashes or night sweats [38]. Finally, although some studies showed oral contraceptive use to be associated with a lower risk of colorectal cancers [42, 43], no clear association was found with colorectal cancer or its subsites in our study.

A few studies have applied Mendelian randomization (MR) method to explore the potential causal relationship between reproductive factors and lung cancer or colorectal cancer. MR study uses genetic variants as a natural experiment to investigate the causal relations between modifiable risk factors and health outcomes [44]. Since the genetic variants in offspring are randomly distributed at conception, confounding and reverse causation are less likely to occur in MR analyses than in observational studies. A MR study suggested that older age at first birth decreased the risk of lung cancer, lung adenocarcinoma specifically [45]. However, they also found that older age at first birth was genetically correlated with high education and lower BMI, which may be regarded as possible confounding factors between age at first birth and cancer risk [45]. Thus, the direct causal effect of age at first birth, if any, on the risk of lung cancer or other cancers should have been obtained by using multivariable MR methods in which socio-economic and lifestyle factors can be taken into account. Another MR study showed no evidence for a causal relationship between age at menarche or age at menopause and colorectal cancer risk [46]. The study had limited power to detect weak effects. Therefore, more MR studies are warranted to investigate the potential causal associations between female reproductive factors and cancer risks in general, especially to confirm the findings generated from the current study between age at menarche and lung adenocarcinoma as well as between number of children and colon cancer.

Potential Mechanisms

Our findings seemed to be in line with our hypotheses, ie, reproductive factors reflecting a lifetime exposure to higher levels of endogenous estrogen may increase the risk of lung and colorectal cancers in women.

Menarche, defined by the onset of menstruation in women, is due to increased estradiol production in puberty [47]. Younger age at menarche may imply more menstrual cycles over the lifetime and hence higher exposure to endogenous estrogen [48]. Exposure to higher levels of endogenous estrogen may be involved in the etiology of lung cancer, especially for lung adenocarcinoma that is not strongly influenced by smoking [6]. Lung tumor proliferation is a process that can be triggered by hormonal receptors including estrogen, progesterone, and epidermal growth factor receptors [49]. These receptors are expressed in both cancerous and noncancerous lung tissues, and they have regulatory effects on tumor growth and proliferation [17, 19, 50]. Progesterone receptors seemed to have tumor-suppressive effects [51] and ERs to stimulate tumor proliferation [17]. More precisely, ERβ may promote estrogen-dependent growth of lung cancer cells [52]. However, the biological mechanisms linking ERβ and lung cancer risk are still unclear.

Pregnancy leads to significant changes in the hormonal milieu, which may be protective against colorectal cancer. For instance, during gestation, production of ovarian estradiol and estrone varies, and the latter becomes the predominant circulating estrogen [53]. Estrone has been shown to significantly decrease proliferation in colonic cancer cell lines [54]. Therefore, a specific hormonal profile during pregnancy in which estrone level is higher may confer a protection against colon tumorigenesis; this may partially explain our observed association between low number of children and increased risk of colon cancer.

Several mechanisms are suggested to be involved in the potential protection of hormone therapy against colorectal cancer. This could be due to an effect on bile acid synthesis and composition or by decreasing synthesis of insulin-like growth factor type I (IGF-I) [55, 56]. This growth factor appears to stimulate proliferation of the intestinal mucosa [57]. In addition, a clinical trial demonstrated that estrogen plus progestin therapy, unlike estrogen alone, was associated with a decreased risk of colorectal cancer [12, 58]. Therefore, progestin may be the protective component in hormone therapy against the risk of colorectal cancer [58].

Overall, biology of sex hormones is complex, and their mechanisms are not clearly elucidated. Exposure to fluctuating levels of hormones for years might play different roles in different tissues, according to their specific hormone receptors.

Strengths and Limitations

Our prospective study is the first one in the Nordic countries to investigate potential associations of a large panel of reproductive factors with the incidences of lung and colorectal cancers. We had a long follow-up duration of over 20 years among a large and homogeneous (97% people with European ancestry) study population [59]. We also had comprehensive information on covariates at baseline, which made it possible to reduce confounding. The information on cancer cases from the Cancer Registry of Norway is accurate and

complete [30]. In addition, the long follow-up duration minimized the possibility of reverse causation for our observed associations between early age at menarche and lung adenocarcinoma and between number of children and colon cancer. Sensitivity analyses after exclusion of the first 3 years of follow-up demonstrated that reverse causation was unlikely to be a problem for the association between hormone therapy and rectal cancer.

Our study has several limitations. First, selection bias cannot be excluded. Comparing the included with the excluded women due to missing information on the reproductive factors (the largest missing was 12%), the excluded women tended to be older, had more incident cases of cancer and less family history of cancer. This might have resulted in more conservative results in our study. Second, data on exposure variables and lifestyle factors were subject to misclassification due to self-reporting, for example for age at menarche. However, it has been shown in the Tromsø Study that menarche age was reported by middle-aged women with good reliability [60]. In addition, missing data on baseline characteristics were classified as an unknown category. Both the misclassification and missing data could have resulted in residual confounding. Nonetheless, results before and after multiple imputation were similar. Third, due to the relatively small sample size, each of the exposure variables of interest was classified into 2 categories. The cutoff value for classifying the 2 categories was chosen in a systematic manner (mean + 1 SD or mean – 1 SD). We also repeated the analyses using age at menarche and number of children as continuous variables and the results were supportive to our main findings. Fourth, residual confounding by smoking in the observed early age at menarche-lung adenocarcinoma association was less likely due to following reasons: (1) smoking was adjusted with detailed information on smoking status and pack-years; (2) after multiple imputation for missing data in all covariates including smoking, results were similar; (3) the distribution of ever smokers was similar between women with early or late menarche; and (4) the smoking prevalence in Norwegian women has decreased over the last decades [61]. Fifth, our findings related to colorectal cancer may have been confounded by diets, especially red meat and processed food consumptions [62], for which there was no information in the HUNT data. However, the E-values calculated in our sensitivity analysis showed that unmeasured confounding had to be quite large to explain away the observed associations between number of children and colon cancer as well as between hormone therapy and rectal cancer. Sixth, our observed associations should be interpreted cautiously due to the multiple exposures and outcomes, increasing the multiple testing burden. Finally, participants were mainly people with European ancestry, which might reduce the generalizability to other ethnic populations.

Conclusion

In this population of Norwegian women, we observed that early menarche was associated with an increased incidence of lung adenocarcinoma, although smoking is the most important risk factor. Low number of children was associated with an increased incidence of colon cancer. Hormone therapy was associated with a decreased incidence of rectal cancer. Further investigations are warranted to study if these are causal associations.

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Author Contributions

M.D. conducted statistical analyses, interpreted results, and wrote the initial draft of the manuscript. Y.Q.S. and X.M.M. contributed to the study design and statistical analyses. X.M.M. and A.L. were responsible for data collection. All authors participated in the data interpretation, contributed to the manuscript writing with important intellectual content, and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

All participants gave their informed consent for participation in HUNT. The current study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (REK sør-øst 2019/337). The study was performed in accordance with the Declaration of Helsinki.

Disclosure Summary

The authors have nothing to disclose.

Disclaimer

Data from the Cancer Registry of Norway (CRN) has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by CRN is intended nor should be inferred.

Data Availability

Data from the HUNT Study that are used in research projects will, when reasonably requested by others, be made available on request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information describes the policy regarding data availability (https://www.ntnu.edu/hunt/data).

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