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Original Research

Menopausal hormone therapy and cancer risk: An overestimated risk?

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Abstract ***Aim:*** We aimed to assess the overall cancer risk among contemporary menopausal hormone therapy (MHT) users in Sweden and the risk for different cancer types.
Methods: A nationwide Swedish population-based cohort study including all 290,186 women aged ≥ 40 years having used systemic MHT during the study period (July 2005 and December 2012), compared with the Swedish female background population. MHT ever-use (all MHT, oestrogen-only MHT [E-MHT] and oestrogen plus progestin MHT [EP-MHT]) was based on the nationwide Prescribed Drug Registry. Cancer diagnoses were grouped into 16 different anatomical locations, for which standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated.
Results: The SIR of any cancer was 1.09 (95% CI: 1.07–1.11) following ever MHT, 1.04 (95% CI: 1.01–1.06) for E-MHT and 1.14 (95% CI: 1.12–1.17) for EP-MHT. The highest SIR was found for EP-MHT among users aged ≥70 years (SIR = 1.33, 95% CI: 1.26–1.40). The risk for invasive breast, endometrial or ovarian cancer combined was increased for any MHT (SIR = 1.31, 95% CI: 1.28–1.34). The risk of invasive breast cancer was increased following MHT and increased with age for EP-MHT users. The risk of gastrointestinal cancers

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combined was decreased (SIR = 0.90, 95% CI: 0.86–0.94), particularly the oesophagus (SIR = 0.81, 95% CI: 0.64–1.00), liver (SIR = 0.81, 95% CI: 0.65–0.99) and colon (SIR = 0.90, 95% CI: 0.84–0.95).

Conclusions: MHT, notably EP-MHT, was associated with a limited increase in overall cancer risk. The increased risk of female reproductive organ cancers was almost balanced by a decreased risk of gastrointestinal cancers.

1. Introduction

Menopausal hormone therapy (MHT) became available approximately 60 years ago. In Sweden, oral oestrogen-only MHT (E-MHT) was first licenced in 1956 (conjugated oestrogens), and the first oral combination with progestin (EP-MHT) in 1976 (levonorgestrel/oestradiol) [1]. Towards the end of the 1990s, Sweden was among the top consumers of MHT in Europe [2], with approximately 32% users [3,4]. Yet, global MHT use has declined substantially over the past few decades, following studies showing an increased risk of some cancer types and cardiovascular events [5–7]. In the United States, the number of prescriptions of E-MHT and EP-MHT has dropped as much as 80% following the release of Women's Health Initiative trial results in 2002 [5,8]. In Sweden, the use of MHT has dropped 30% to approximately 7% in 2010 [2,9].

Meta-analyses indicate that MHT is associated with an increased risk of breast and possibly ovarian cancer [10,11]. Current evidence associates E-MHT with an increased risk of endometrial cancer, but it is less clear if combined EP-MHT can eliminate this excess risk [12]. A reduced risk has been indicated for some gastrointestinal cancers [13–18], yet for other cancer types the evidence is inconsistent [19–23]. Most studies have examined only one cancer type and grouped different MHT regimens together, sometimes also including non-systemic MHT. Moreover, there has been a great variation in the definition of MHT use and in the age of the study populations across studies [10,24].

Whilst detailed studies of individual cancer sites are crucial for causal inference, data on the net effect of MHT on total cancer risk are relevant for counselling and management of women with menopausal related symptoms [7,8]. To our knowledge, population-based studies assessing the overall risk of cancer in users of contemporary formulations of systemic MHT are non-existent. With the aim to cover this gap of knowledge, we used data from the nationwide registers of dispensed drugs and incident cancers in Sweden.

2. Methods

This study followed an a priori defined study protocol and was based on a large, nationwide cohort, which has been described in detail elsewhere [13,18]. All 290,186 Swedish women aged ≥ 40 years at first recorded prescription (index date) who received ≥1 dispensed prescription of systemic MHT between 1st July 2005 and 31st December 2012, according to the Swedish Prescribed Drug Registry were included. This registry covers all prescribed and dispensed drugs for Swedish residents since July 2005 and was used to extract Anatomical Therapeutic Chemical (ATC) Classification codes, prescription and dispense dates [25]. The Cancer Registry (initiated in 1958, >96% complete) was used to obtain information on date and anatomical location of all newly diagnosed cancers [26]. The Swedish Causes of Death Registry (initiated in 1952, 100% complete) was used to retrieve the date of death [27]. Women with a history of any malignancy (apart from non-melanoma skin cancer) were excluded. MHT ever-users were compared with the entire Swedish source population (≈2.5 million women). Data on the total background population (by age, sex and calendar period) were retrieved from the Swedish Registry of the Total Population and Cancer Registry. The Stockholm Regional Ethical Review Board approved the study (2014/1291-31/4), without need for informed consent.

2.1. Exposure

Ever-use of systemic (oral or transdermal) MHT was defined according to relevant medication codes in the ATC system: oestrogens (G03C), progestins (G03D if combined with G03C) and oestrogens plus progestins (G03F; subdivided to continuous [G03FA] and sequential [G03FB] combinations) and categorised as E-MHT (oestrogen only) or EP-MHT (oestrogen users with ≥1 prescription of progestin during the study period). For users of G03F combinations, >99% received oestradiol. For subgroups of E-MHT (oestradiol, oestriol or tibolone) and EP-MHT (continuously or sequentially administered progestin; progesterone- or testosterone-derived progestins), those receiving different MHT types or regimens were excluded. We used the World Health Organisation 'daily-defined dose' per package to estimate the duration, taking into account the potency and prescribed quantities of the drug.