MEN1-Dependent Breast Cancer: Indication for Early Screening? Results From the Dutch MEN1 Study Group

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Objective: Multiple endocrine neoplasia type 1 (MEN1) is associated with an early-onset elevated breast cancer risk. This finding potentially has implications for breast cancer screening for women with MEN1, and therefore it is necessary to assess whether other risk factors are involved to identify those at greatest risk.

Design: A cross-sectional case control study was performed using the Dutch MEN1 cohort, including >90% of the adult Dutch MEN1 population. All women with a confirmed *MEN1* mutation received a questionnaire regarding cancer family history and breast cancer–related endocrine and general cancer risk factors.

Results: A total of 138 of 165 (84%) eligible women with *MEN1* completed the questionnaire. Eleven of the 138 women had breast cancer. Another 34 relatives with breast cancer were identified in the families of the included women, of whom 11 were obligate *MEN1* carriers, 14 had no *MEN1* mutation, and 9 had an unknown *MEN1* status. The median age at breast cancer diagnosis of women with *MEN1* (n = 22) was 45 years (range, 30 to 80 years), in comparison with 57.5 years (range, 40 to 85 years) in female relatives without MEN1 (n = 14; $P = 0.03$) and 61.2 years in the Dutch reference population. Known endocrine risk factors and general risk factors were not different for women with and without breast cancer.

Conclusion: The increased breast cancer risk in *MEN1* carriers was not related to other known breast cancer risk factors or familial cancer history, and therefore breast cancer surveillance from the age of 40 years for all women with *MEN1* is justifiable. **(*J Clin Endocrinol Metab* 102: 2083–2090, 2017)**

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Abbreviations: CAT, computer-assisted tomography; DMSG, Dutch MEN1 study group; MEN1, multiple endocrine neoplasia type 1.

Carrying a mutation in a gene that gives rise to an increased breast cancer risk leads to distress in patients and may necessitate breast cancer screening from a younger age. Recently, our group reported that the *MEN1* gene predisposes for early-onset breast cancer in female carriers. Multiple endocrine neoplasia type 1 (MEN1)-related breast tumors showed loss of the wild-type *MEN1* allele, suggesting a cell-autonomous and *MEN1* gene–dependent tumorigenic mechanism (1). This was further strengthened by the observation that silencing of the *MEN1* gene results in proliferative gene expression changes in primary mammary luminal progenitor cells in human breast tissue (2). Considering the impact on patients and the potential need of changing the current guidelines regarding early breast cancer surveillance, further research is indispensable to identify potential additional risk factors that might have influenced this result (3).

A mutation in the *MEN1* tumor-suppressor gene leads to MEN1, which is classically characterized by the combined occurrence of parathyroid adenomas, pituitary adenomas, and duodenopancreatic neuroendocrine tumors (4, 5). The prevalence of MEN1 is 3 to 4/100,000, which underlines the rarity of the disease (6). Performing association studies for a rare disease in this population is therefore challenging, and cautiousness in formulating advice on breast cancer surveillance should be regarded.

The relative risk for breast cancer for women with MEN1 of 2.83 (1) categorizes the *MEN1* gene as a moderate risk factor for breast cancer (7). Women with an increased breast cancer risk may benefit from intensified screening from an earlier age and possibly at shorter intervals than women at average risk (8). Screening is associated with a reduction in breast cancer mortality of ~35% to 70% in different European studies (9–11). However, breast cancer surveillance also gives rise to a risk of false-positive findings, resulting in unnecessary biopsies, especially when screening starts at a younger age (12, 13). When weighing the potential benefits and harms of screening, the important question arises from which age and interval women with MEN1 should be screened.

The mean age at breast cancer diagnosis was 48 years for the Dutch MEN1 population and 51 years for three validation cohorts (1). This is 10 years earlier than the median age of 61.2 years at breast cancer diagnosis for women in the general Dutch population and underlines the young breast cancer onset in women with MEN1.

In formulating advice, known breast cancer risk factors such as lifestyle factors (14, 15), endocrine-related risk factors (16), and a high occurrence of breast cancer in the family should be considered. These risk factors should be considered, which is challenging given the small sample size of the cohorts of patients with MEN1 as a consequence of the rarity of the disease. Nevertheless, the elevated relative risk and younger age of onset justify further research. Therefore, the initial aim of this study was to assess the role of familial breast cancer risk, lifestyle, and endocrine-related risk factors in the higher risk for breast cancer in women with MEN1. The second aim was to formulate a recommendation on screening for daily clinical practice of MEN1 care.

Methods

Study design and patients

Female patients were selected for this study from the Dutch MEN1 study group (DMSG) database. This longitudinal database includes >90% of all Dutch patients with MEN1, aged 16 years and older at the end of 2013, treated at one of the Dutch University Medical Centers between 1990 and 2013. Women with a *MEN1* mutation or a clinical MEN1 diagnosis from a family with a confirmed *MEN1* mutation were eligible for this study. We performed a cross-sectional case control study from April 2015 to October 2016 in which eligible women were invited to complete a questionnaire.

All women who participated in the study provided written informed consent. The Medical Ethical Committees of all Dutch University Medical Centers in the Netherlands confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study, and therefore an official approval was not required under WMO.

Questionnaire

The questionnaire was completed by hand or on line. The questionnaire addressed the following topics.

Medical history

Respondents were asked whether they had breast cancer and when it was diagnosed.

Family history

Participants were asked to fill out which family members had non–MEN1-related cancer and whether these family members were *MEN1* carriers. This was specifically asked for their first- and second-degree relatives.

Lifestyle factors

Current and past smoking status was assessed by inquiring the years and type of smoking (cigarettes/cigars). Regarding alcohol consumption, we asked about consumption per decade, start of alcohol consumption, and quantity of consumption. Weight and history of weight change were determined. Height was self-reported and used to calculate body mass index.

Endocrine-related factors

Women were asked to complete questions about age at menarche, oral contraceptive use, pregnancies, breast feeding, and hormone replacement.

Family history

We constructed pedigrees for each participant/respondent. Accuracy of the family relationships and medical data of the relatives was verified through the pedigrees of the MEN1 families that are documented in the medical records at the department of internal medicine or clinical genetics (17). The pedigrees focused on MEN1 and breast cancer. Participants filled out which family members had breast cancer and if those family members were diagnosed with MEN1.

Age at breast cancer diagnosis

To compare the age at breast cancer diagnosis of our cohort with the age of breast cancer occurrence of the general Dutch population, data were retrieved from the Netherlands Cancer Registry, which is hosted by the Netherlands Comprehensive Cancer Organization. The age of breast cancer onset of women with MEN1 and their female relatives without MEN1 was assessed to study if an early age of breast cancer onset was a familial predisposition or exclusively related to MEN1. The age of breast cancer occurrence of family members who were not included in our DMSG database was reported by the respondents. These family members were non-*MEN1* carriers, *MEN1* carriers not living in the Netherlands, or deceased (otherwise these patients would have been included in the database).

Statistical analysis

Descriptive statistics were used to characterize the study population, to determine the age of breast cancer onset, and to examine the difference between women with and without breast cancer. For this cross-sectional case control study, women with *MEN1* were cases, and women with *MEN1* but without breast cancer were used as controls. Although this is a case-control study, odds ratios are not calculated because prevalent cases are presented wherein the odds ratio is not representative for the risk ratio. Independent sample *t* tests or Mann-Whitney *U* tests for continuous variables and the χ^2 tests or Fisher's exact tests for categorical variables compared potential risk factors between women with and without breast cancer.

Results

Response rate

A total of 210 women with MEN1 were identified, of whom 45 (21.4%) were ineligible for inclusion because they only had two MEN1-related major manifestations, but none had a confirmed *MEN1* mutation or family members with a *MEN1* mutation, were not in follow-up at time of data collection, or had died. Of the 165 eligible women, three refused to participate, eight women could not be reached, and three women died during data collection. Of the remaining 151 women, a total of 138 completed the questionnaire, giving a response rate of 84% (Fig. 1).

Familial breast cancer

Respondents were from a total of 64 families, with a median of two respondents (range, 1 to 12 respondents) per family. Eleven respondents with breast cancer and MEN1 were from 10 different families. According to the Dutch guidelines, additional *BRCA1/2* and *CHEK1* mutation analyses were performed in a family with two cases, of whom both mutations were negative. Through the family histories of all the respondents, 11 additional obligate *MEN1* carriers with breast cancer from 11 families were identified. A total of 21 (33%) families had patients with breast cancer and MEN1. Sixteen (73%) women with breast cancer and MEN1 had no family members with breast cancer. Five women had a single family member with MEN1 and breast cancer. In two different families, there were two first-degree relatives with MEN1 and breast cancer. In one of these families, *CHEK2* and *BRCA* were tested and found to be negative. In one family, there were two second-degree family members, one with breast cancer and MEN1 and one with breast cancer at the age of 80 years for whom the *MEN1* status was unknown. One family member with breast cancer, identified by the questionnaire, had *BRCA1* but was not a carrier of the *MEN1* gene.

Comparison of risk factors between respondents with and without breast cancer

Although there were some small differences between the groups, no significant and clinically relevant differences in breast cancer risk factors between the respondents with and without breast cancer were observed (Table 1). All women were white, and none had a prolactinoma.

Age at breast cancer diagnosis

Eleven respondents with a confirmed *MEN1* gene mutation had been diagnosed with breast cancer and were included in the DutchMEN database. The breast cancer diagnosis was based on pathology reports. The median age at diagnosis was 44 years (range, 34 to 64 years). Another 34 women with breast cancer were identified through the family history of the respondents. Eleven of those women were obligate *MEN1* carriers, 14 had breast cancer but did not have *MEN1*, and nine had an unknown *MEN1* status.

The median age at breast cancer diagnosis of the total of 22 women with MEN1 (confirmed *MEN1* gene mutation and obligate carriers) was 45 years (range, 30 to 80 years), in comparison with a median age of breast cancer onset of 57.5 years (range, 40 to 85 years) ($P = 0.03$) in the relatives who did not have a *MEN1* mutation. The mean age at breast cancer diagnosis in the Dutch population was 61.2 years from 2009 to 2013 (18). Five out of 35 women with MEN1 having a negative *MEN1* mutation test had breast cancer, resembling the chance of breast cancer for women from the general Dutch population. One of those women had a prolactinoma before breast

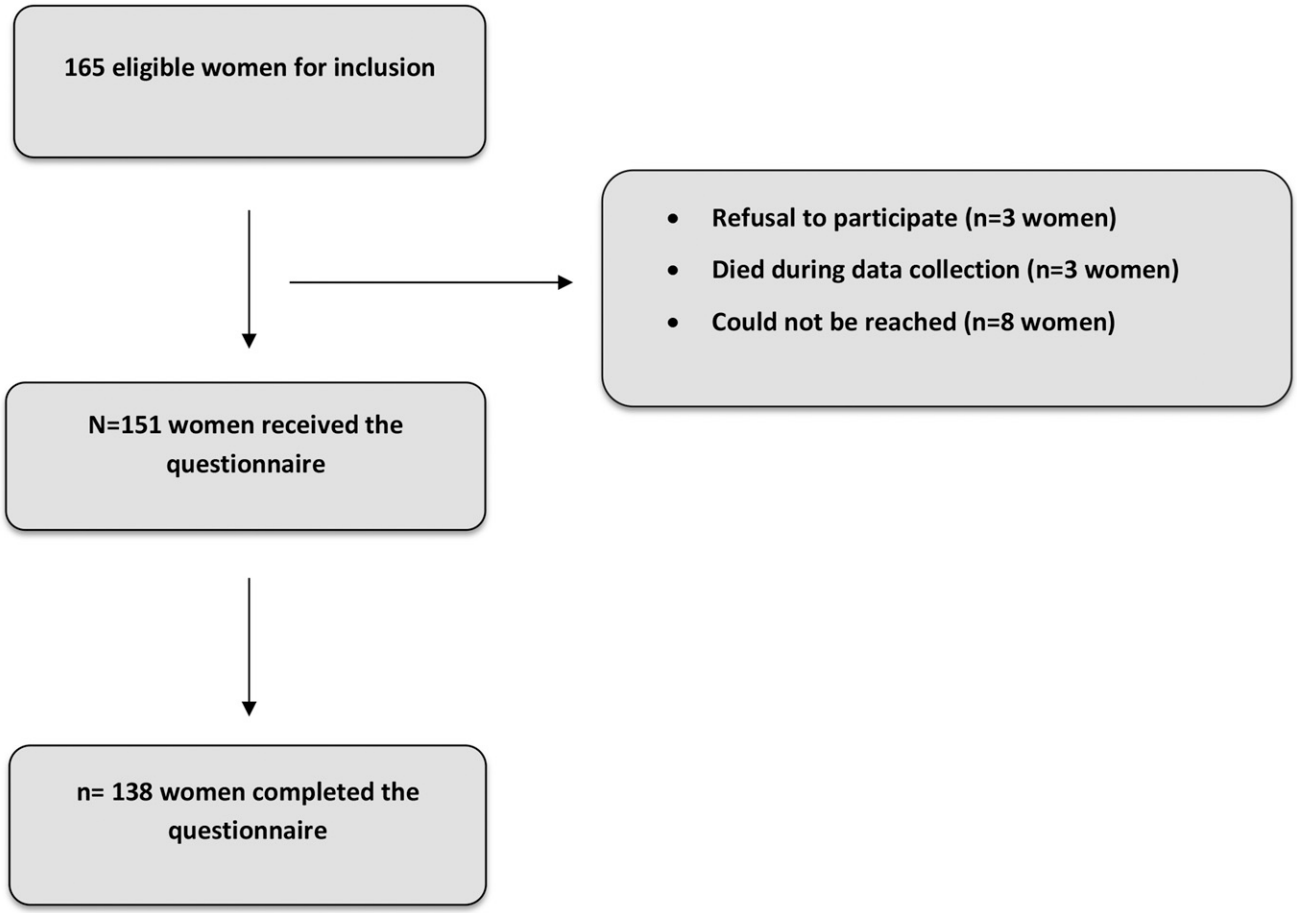

Figure 1. Flowchart of the study population.

cancer diagnosis. The median age of breast cancer in those patients was 60 years (range, 48 to 69 years), which is in line with the women in the general Dutch population.

Discussion

In the current study, based on a valid representation of all known Dutch MEN1 families corresponding to a response rate of 84%, predisposing general and reproductive risk factors were equally present in women with MEN1 with and without breast cancer. In the majority of cases, familial breast cancer was not present. By identifying 11 additional MEN1-related breast cancer cases, we confirmed that that the age of breast cancer onset is significantly lower in women with MEN1 than without MEN1.

Familial breast cancer risk can be modified by other risk factors, such as age at menarche and menopause, age at first child birth, parity, oral contraception use, breast feeding, alcohol consumption, and smoking (19–25). Patients with breast cancer could have had more predisposing factors for breast cancer than control subjects (16). However, Table 1 reflects that there were no major differences between cases and control subjects that predispose for breast cancer. Small, nonsignificant differences between cases and control subjects were found for breastfeeding, in which cases had breastfed 2 months longer than control subjects. Each year of breastfeeding reduces the breast cancer risk by 4.3%, in addition to the risk associated with each birth (26). Furthermore, a higher percentage of cases had ever smoked, but the reported duration of smoking was longer in control subjects. Cases started smoking at a younger age than control subjects. An increased breast cancer risk has been found in women who smoke between menarche and first full-term pregnancy (27, 28). Frequent radiation exposure by surveillance with computer-assisted tomography (CAT) scans as part of MEN1 screening could potentially increase breast cancer risk. In this respect, CAT scans can be considered a confounder, and therefore the frequency of CAT scans was compared for women with and without breast cancer. This number was equal for both groups, and therefore this risk seems marginal.

The age of breast cancer diagnosis of mutation-negative women with MEN1 was not different from

Table 1. Comparison of General and Reproductive/Endocrine Factors in Women With MEN1 With and Without Breast Cancer

	Breast Cancer (n = 11)	No Breast Cancer (n = 127)	*P* Value
Age at menarche, y	13 (12–14)	13 (9–18)	0.6
Parity	2.0 (0–3)	2.0 (0–7)	1.0
Nulliparity, %	36	33	1.0
OAC before age 20, %	50	72	0.2
Duration OAC, y	11 (2–26)	10 (1–36)	0.9
Age at menarche, y	13 (12–14)	13 (9–18)	0.6
Total duration of breast feeding, mo	5 (0–12)	3 (0–52)	0.4
Age at first birth, y	26 (20–31)	27 (19–40)	0.5
BMI at inclusion	23 (17–32)	24 (19–41)	0.3
BMI at age 18	20.8 (18–25)	21 (16–29)	0.8
Smoking ever,[a] %	55	41	0.4
Smoking, age at start, y	16 (14–25)	16 (12–29)	0.4
Smoking duration, y	11 (2–29)	16 (4–49)	0.3
Age at first alcohol use, y	18 (16–20)	16 (12–50)	0.1
Never used alcohol, %	18	20	0.6
CAT scans (thoracic), n	2 (1–9)	2 (1–14)	1.0

Data are presented as median ± range or percentage. *P* values are derived from χ^2 or Fisher exact tests and independent-sample *t* test or Mann-Whitney *U* test.

Abbreviations: BMI, body mass index; CAT, computer-assisted tomography; OAC, oral anticonception.

[a] More than one cigarette per day for >1 year.

the general Dutch population. This outcome confirms the findings of a previous study in which mutation-positive patients with MEN1 had a different phenotype when compared with mutation-negative patients (29).

Limitations

The small sample size of this study is a limitation, especially in finding significant differences in risk factors between women with and without breast cancer. Only large effects can be detected with a small sample size, which is reflected by the limited power. However, to our knowledge, this is, to date, the largest cohort in which this topic has been studied, and we aimed for identifying strong risk factors that may modify the relation between MEN1 and breast cancer. In line with the retrospective nature of this study, other low- and moderate-penetrance breast cancer genes, such as *CHEK2*, were not tested in all respondents with breast cancer because it was not the standard of care at time of genetic counseling. This can be considered another limitation. The guidelines regarding genetic testing in women with breast cancer were revised in the Netherlands in 2014, and since then *CHEK2* has been routinely tested. According to the guidelines, women included in the current study who were eligible for additional testing for the *CHEK2* mutation were tested and did not have this mutation. The rationale for *CHEK2* mutation testing is the occurrence of the *CHEK2**1100delC mutation in 1% of the general Dutch population and in 5% of women with breast cancer (30). At this time, genetic testing for other low- and moderate-penetrance breast cancer genes is not the standard of care. Another potential concern is the recall bias, which refers to systematically overreporting or underreporting of exposure to risk factors in women with breast cancer in comparison with women without breast cancer. Previous case-control studies assessing the association between risk factors and breast cancer have concluded that there was minimal recall bias in reporting alcohol consumption and physical activity (31, 32).

Strengths

A major strength of this study is the population-based DMSG database, which consists of >90% of the total Dutch MEN1 population. The occurrence of selection bias is therefore minimized by the high coverage of patients with MEN1. Subsequently, the high response rate of 84% contributes to the reliability and validity of the study results. This is the largest MEN1 cohort in which this topic has been studied, which makes the data unique. The women who were identified by the questionnaire were not included in the database because they either had died or did not live in the Netherlands. This confirms the rigorous manner of identifying of all patients with MEN1 who are currently under medical care in the Netherlands by the DMSG database.

Familial breast cancer risk is an important risk factor that is reflected by its inclusion in different screening assessment tools, such as the Claus, BOADICEA, and Tirer-Cusick models, in estimating breast cancer risk (33–35). Familial breast cancer and MEN1 carriership were assessed thoroughly in the questionnaire, and the accuracy was verified by pedigrees present at the

department of internal medicine and genetics. Because more family members of one family filled out the questionnaire, the accuracy of the family trees could be checked. The accuracy of family histories provided by women on reporting breast cancer family history is generally reliable (36). By comparing the age of breast cancer onset in non-MEN1 female relatives to women with MEN1, the optimal controls were created to adjust for another familial risk factor, which can be considered a major strength.

Breast cancer surveillance in women with MEN1

The purpose of breast cancer screening is to reduce breast cancer–specific mortality and the incidence of advanced breast cancer. The incidence and mortality risk of breast cancer in the Netherlands were 172/100,000 and 35.5/100,000 in 2014, respectively. On average, there is a relative reduction of 50% in mortality from breast cancer in women who undergo mammographic screening (9–11).In formulating advice on breast cancer screening, treatment-related morbidity and the harms of screening are considered (37). The national breast cancer screening program in the Netherlands consists of biennial screening mammography for women aged 50 to 74 years (38). This is in line with most European countries and the recommendation of the US Preventive Services Task Force (38, 39). Considering the median age of 45 for breast cancer diagnosis in women with MEN1, the question arises of whether the current screening program applies to this population. For women aged 40 to 74 years with an average breast cancer risk, there is evidence that screening by mammography reduces breast cancer mortality, but there is also considerable harm in this group due to diagnosis and treatment of noninvasive breast cancer that would not have become life threatening or to clinical attention in the woman's lifetime in the absence of screening. False-positive results as a consequence of overdiagnosis leads to unnecessary and invasive follow-up (13).

Mandelblatt *et al.* (12) studied the harms and benefits of eight different screening strategies by using different simulation models and found that annual screening from the age of 40 years in women with a twofold to fourfold increase in breast cancer risk had similar or even more favorable harm/benefit ratios as biennial screening of women with average-risk from 50 to 74 years of age. This seems directly applicable for women with MEN1 with a relative risk of 2.8 and a median age at diagnosis of 45 years. However, as part of surveillance for MEN1, women with MEN1 undergo a stringent screening program to detect MEN1-related tumors. The addition of another screening modality will increase the burden. Moreover, the tumors can be characterized as prognostically "favorable" because the majority of tumors of initial cases were luminal-type breast cancers. Only one woman had a triple-negative breast tumor (1). Considering this, one may question if women with MEN1 should be screened from an earlier age. Interestingly, 60% of women with breast cancer were premenopausal at time of breast cancer diagnosis, which is in line with the younger age at diagnosis.

Clinical implications: to screen or not to screen?

The findings of the current study highlight the need for adaptation of the clinical guidelines regarding breast cancer screening. The small population, and consequently the limited power, make it difficult to formulate a strong recommendation. However, in this extended cohort and in three independent international cohorts (1), the younger age at breast cancer diagnosis has been confirmed. This early age of breast cancer onset, which is at least 12 years earlier than the general population, can therefore not be neglected. In addition, based on the results, there is no indication that breast cancer was caused by other risk factors or familial risk. A suggested age to start screening is from the age of 40 years biennially. This is almost 10 years before the mean age of breast cancer in our cohort and in concordance with the Dutch screening program that starts at the age of 50 years, which is 10 years before the mean age of breast cancer in the general Dutch population.

In our view, a biennial screening program from the age of 40 is justifiable because the majority of breast tumors were of luminal type and can therefore be considered prognostically favorable (1). In addition, the burden of an annual screening program can therefore be avoided. Large international collaborations are needed to assess the effect of breast cancer screening in women with MEN1 for whom the prevention of progressed breast cancer by early diagnosis is weighed against the potential harms as a consequence of overdiagnosis and unnecessary invasive follow-up.

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